ALABAMA MEDICAID AGENCY
P&T Meeting
Preferred Drug Status Reviews
August 6, 2003

PHARMACOTHERAPY REVIEWS

ANTIANXIETY AGENTS

I. INTRODUCTION

The search for safe and effective antianxiety agents is centuries old. Prior to 1980 and the development of DSM-III diagnostic criteria, the classification of anxiety disorders was broad and vague. Alcohol, bromides and paraldehyde were early anxiolytics. They were largely replaced by barbiturates early in the 20th century. Due to toxicity and dependence problems, barbiturates were largely abandoned in favor of anxiolytics such as the nonbarbiturate, meprobamate (c.1950). The first benzodiazepine anxiolytic (chlordiazepoxide) appeared in the late 1950s and many others followed. Many other agents that do not have anxiety management as their primary indication (e.g., antidepressants) have been found to have significant anxiolytic properties.

This review focuses upon agents that are generally recognized by the drug information compendia and practicing clinicians as antianxiety agents per se. These agents are included in Table I.

TABLE I -- ANTIANXIETY AGENTS REVIEWED

Drug	Strength (mg)	Dosage Form
BENZODIAZEPINES		
*Chlordiazepoxide**	5.0	Capsule
	10.0	Capsule
	25.0	Capsule
Chlordiazepoxide (Libritabs®)	10.0	Tablet
	25.0	Tablet
*Diazepam**	2.0	Tablet
	5.0	Tablet
	10.0	Tablet
*Lorazepam**	0.5	Tablet
	1.0	Tablet
	2.0	Tablet
Oxazepam*	10.0	Capsule
	15.0	Capsule
	30.0	Capsule
	15	Tablet
AZASPIRONE		
*Buspirone**	5.0	Tablet
	7.5	Tablet
	10.0	Tablet

	15.0	Tablet
	30.0	Tablet
Buspirone (BuSpar Dividose®)	15.0	Tablet
	30.0	Tablet

TABLE I -- ANTIANXIETY AGENTS REVIEWED		
Drug	**Strength (mg)**	**Dosage Form**
MISCELLANEOUS AGENTS		
*Doxepin**	10.0 25.0 50.0 75.0 100.0 150.0	Capsule Capsule Capsule Capsule Capsule Capsule
*Hydroxyzine HCl**	10.0 25.0 50.0	Tablet Tablet Tablet
Hydroxyzine HCl (Atarax 100®)	100.0	Tablet
*Hydroxyzine Pamoate**	25.0 50.0 100.0	Capsule Capsule Capsule
*Hydroxyzine HCl**	10/5ml	Syrup
Hydroxyzine Pamoate (Vistaril®)	25/5 ml	Oral Susp
*Meprobamate**	200 400	Tablet Tablet

*Items in red are multisource versions. All multisource products are automatically exempted from any prior authorization requirement.
Note: All strengths and dosage forms of clorazepate currently requires prior authorization. Alabama Medicaid does not provide coverage for alprazolam in brand or generic forms.

II. ANXIETY DEFINED

Anxiety is an emotional state commonly caused by the perception of real or potential danger that threatens the security of an individual.[1] Clinical anxiety is not to be confused with unavoidable situational nervousness and apprehension associated with stress. Such responses are usually transient.

True anxiety disorders are, however, the most frequently occurring mental disorders. Proper diagnosis and management of anxiety disorders is crucial if negative outcomes are to be avoided.

III. INCIDENCE OF ANXIETY DISORDERS

Anxiety disorders, when considered collectively as a heterogeneous group, are not uncommon. It is estimated that one-fourth of the population will experience at least one anxiety disorder of some duration in a lifetime. The 12-month prevalence rate for anxiety disorders averaged 17.2% and the lifetime rate averages 24.9%.[2]

Social anxiety disorder (SAD) is the most common anxiety disorder followed by generalized anxiety disorder (GAD). Anxiety disorders typically occur before age 30 and are more common in women and those with a family history of anxiety and/or depression. While most anxiety disorders are chronic in nature, symptoms may remit and exacerbate. Long-term treatment may be required, and relapses after drug discontinuation are not uncommon.[3]

IV. ETIOLOGY/PATHOPHYSIOLOGY

A true anxiety disorder is challenging to differentiate as a number of medical conditions are associated with anxiety (see Table II). Anxiety symptoms may also be a coexisting symptom associated with major psychiatric disorders (e.g., schizophrenia, dementia, delirium or drug use (see Table III) and/or drug abuse.

TABLE II ---
SELECTED MEDICAL DISORDERS ASSOCIATED WITH ANXIETY SYMPTOMS[3]

Respiratory	Infection, asthma, chronic obstructive pulmonary disease
Cardiovascular	Cardiac rhythm disturbances, heart attack, stroke, deep vein thrombosis, congestive heart failure, coronary artery disease, heart attack, transient ischemic attacks
Metabolic	Diabetes mellitus, hyperthyroidism, hyperkalemia, B_{12} or folic acid deficiency, iron deficiency
Other	Cancer, migraine, seizure disorder, pain syndrome of various etiologies, physical dependency (withdrawal of drug)

The differential diagnosis of anxiety disorders require a complete physical exam, mental status exam, appropriate laboratory testing, a drug screen and a complete medical, psychiatric and drug history (i.e., illegal drugs, prescription drugs, over-the-counter drugs and herbal "therapies").

TABLE III ---
SELECTED DRUGS AND DRUG CLASSES ASSOCIATED WITH ANXIETY SYMPTOMS[4,5]

Stimulants	amphetamines, methylphenidate, caffeine, ephedra, ephedrine, pseudoephedrine, cocaine
Drug-Induced Side Effect (Other)	adrenergics, anticholinergics, anticonvulsants, certain antihistamines, antiparkinsonism drugs, antipsychotic medications, bronchodilators, digoxin, isoproterenol, niacin, corticosteroids, thyroid supplements.

Once medical, psychiatric, drug and drug dependency factors are ruled out as etiological factors, the focus can become the neurochemical basis of anxiety disorders per se. The response to drug
therapy in the management of anxiety disorders is associated with numerous functional units of the brain and several neurotransmitters. Primary neurotransmitters involved appear to be norepinephrine (NE), gamma-aminobutyric acid (GABA) and serotonin (5-HT). They exert their activity at a variety of receptor sites in the central nervous systems (CNS).

The benzodiazepine (BZ) receptor is linked to the GABA type A (GABAa) receptor and a chloride ion channel (the GABA-BZ receptor complex).[1,6] GABA is the major inhibitory neurotransmitter in the CNS and has a strong regulatory or inhibitory effect on 5-HT, NE and dopamine (DA).[1] Different neurotransmitters and different neuropathways and receptor types[6] require different therapeutic approaches to the management of different types of anxiety disorders.

V. CLASSIFICATION OF ANXIETY DISORDERS (DSM-IV-TR)[5]

The classification of anxiety disorders by the American Psychiatric Association (DSM-IV-TR) is included below.

1. Generalized Anxiety Disorder (GAD)
2. Panic Disorder
    a. With agoraphobia
    b. Without agoraphobia
3. Agoraphobia (without a history of panic disorder)
4. Phobic Disorder
    a. Social Phobia (Social Anxiety Disorder)
    b. Specific Phobia
5. Obsessive-Compulsive Disorder
6. Post-Traumatic Stress Disorder (PTSD)
7. Acute Stress Disorder

VI. DIAGNOSTIC CRITERIA FOR SELECTED ANXIETY DISORDERS

DSM-IV-TR diagnostic criteria for the five (5) most common anxiety disorders (i.e., generalized anxiety disorder, panic attack, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder) are attached to this review as Appendix A for the information of the P&T Committee members and Alabama Medicaid.

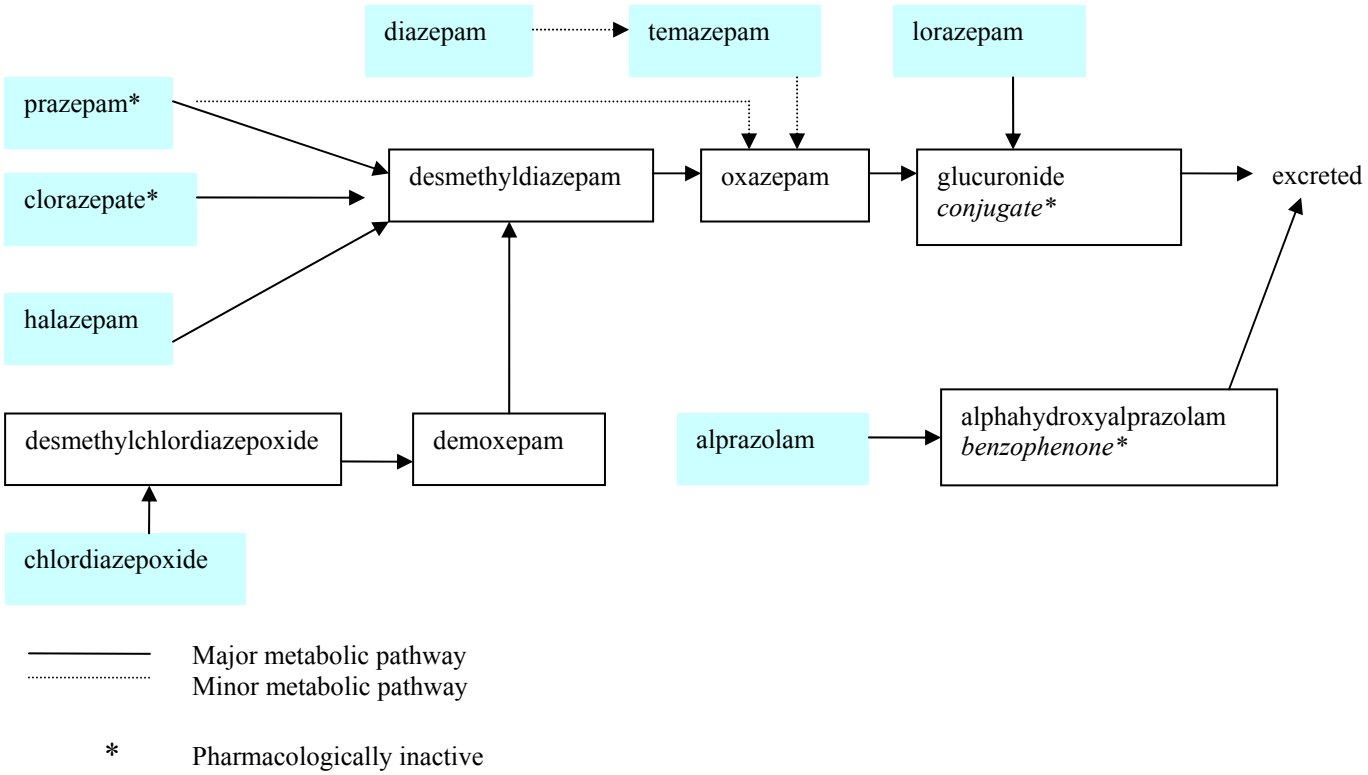
VII. PHARMACOTHERAPEUTIC CHARACTERISICS OF SELECTED ANTIANXIETY AGENTS

Benzodiazepine (BZ) antianxiety agents appear to potentiate the effects of GABA (i.e., facilitate inhibitory GABA neurotransmission) and other inhibitory neurotransmitters, by binding to the BZ receptor sites. There are at least two BZ receptor sites, BZ_1 and BZ_2. BZ_1 is thought to be associated primarily with sleep mechanisms and BZ_2 with cognitive, motor, sensory and

memory functions. The BZ receptors in the limibic and cortical areas are most involved in influencing behavior/anxiety. Anxiolytic properties of benzodiazepines are distinct from
nonspecific consequences of CNS depression (e.g., sedation, motor impairment) at doses approved for anxiolytic effect.

BZ metabolic pathways are included in Table IV. BZs with inactive metabolites are generally preferred in managing anxiety. The benzophenone and glucuronide metabolites are inactive. Desmethyldiazepam is an active metabolite and has a very long half-life (up to 100 to 150 hours in the elderly). Alpha-hydroxy-alprazolam is approximately 50% as active as its parent compound. Oxazepam and lorazepam are metabolized to inactive compounds and offer significant safety features, particularly in the elderly and hepatically impaired.

TABLE IV
BENZODIAZEPINE METABOLIC PATHWAYS



Flow chart reproduced with the permission of Facts and Comparisons, St. Louis, MO. Drug Facts and Comparisons. 2003 (July) 876.

Buspirone is the sole member of a therapeutic subclass of anxiolytics…. the azapirones. Buspirone is a nonsedating, nonbenzodiazepine anxiolytic. Buspirone lacks prominent sedative effects. It has high affinity for serotonin (5-HT_{1A}) receptors but no significant affinity for BZ receptors. Buspirone used chronically is not associated with tolerance, physical or psychological dependence.

Doxepin is a tricyclic antidepressant with an anxiety indication. Doxepin is rarely used to manage anxiety unless depression coexists.

Hydroxyzine is a piperazine derivative. In addition to its anxiolytic activity, hydroxyzine exerts a skeletal muscle relaxant, bronchodilator, antihistaminic, modest analgesic, antispasmodic, and antiemetic effect. Metabolites include cetirizine, marketed as the nonsedating antihistamine, Zyrtec®. Hydroxyzine is rarely used as an anxiolytic because of its nonspecificity.

Meprobamate, an older anxiolytic, has been largely replaced in therapy by other agents due to its side effect profile; history of overuse, misuse and/or abuse; and potential to produce drug dependency.

All anxiolytic agents (see Table I) have the potential to **interact** adversely and significantly with alcohol and a variety of CNS depressants (e.g., narcotics, other anxiolytics, hypnotics, skeletal muscle relaxants).[7,8]

BZs are mostly likely to **interact** adversely and significantly with azole antifungals, antidepressants, macrolide antibiotics, antiretrovirals, rifabutin, rifampin, and rifapentine.[7,8]

Buspirone is most likely to **interact** adversely and significantly with azole antifungals, macrolide antibiotics, calcium channel blockers, rifabutin, Rifampin and rifapentine.[7,8]

Doxepin is most likely to **interact** adversely and significantly with anticoagulants, carbamazepine, carbidopa, cimetidine, clonidine, divalproex, dobutamine, dopamine, ephedrine, epinephrine, guanethedine, H_2 antagonists, MAOIs, phenylephrine, quinolone antibiotics, rifabutin, rifampin, valproic acid and valproate.[7,8]

Hydroxyzine and meprobamate are most likely to **interact** adversely and significantly with other drugs with CNS depressant properties.[7,8]

Relative to **adverse effects**, similarities in adverse effects among the anxiolytics included in Table I will not be presented. Such lists are available in product information/package labeling and will not be duplicated in this report.

VIII. THERAPEUTIC MANAGEMENT

For most patients with an anxiety disorder, even without concomitant depression, antidepressants have emerged as effective therapy and often first-line therapy.[9] SSRI antidepressants are preferred over tricyclic antidepressants because of a more favorable side effect profile.

The benzodiazepines are effective for treating most forms of anxiety but are associated with more side effects than the SSRI antidepressants. Benzodiazepines have limited benefit in obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD).[9]

Buspirone has a more favorable side effect profile than other anxiolytics. Buspirone produces negligible sedation, psychomotor impairment, abuse, dependence withdrawal and is not lethal if overdosed.[10] However, the efficacy of buspirone remains an issue. Buspirone is <u>not</u> effective for the treatment of panic disorder.[11] Most clinicians view buspirone as a relatively weak, slow onset (two weeks), multiple daily dose anxiolytic, but it has shown effectiveness in treating GAD.

While SSRI antidepressants are effective and generally well tolerated in managing a variety of anxiety disorders (e.g., GAD, SAD, OCD, PTSD, panic disorder), they are not well accepted by some patients because of delayed onset of action, sexual dysfunction and/or therapeutic failure. [10]

Neurobiological evidence implicates both serotonin and norepinephrine systems in depressive and anxiety disorders, and tricyclic antidepressants inhibit both serotonin and norepinephrine reuptake. The adverse effect profile of tricyclic antidepressants precludes use over SSRI antidepressants in most cases, however.

BZ anxiolytics remain very important therapeutic agents, especially in severe or acute situations where an immediate anxiolytic effect is required. BZs are effective for most forms of anxiety, and are the most frequently used drugs for treating GAD.[1]

Various sources have acknowledged agents considered most appropriate for the management of anxiety disorders. These are presented below and use of some agents in managing anxiety disorder, although documented in one or more clinical trials, are not yet FDA-approved.[1,9, 15,16]

1. <u>Generalized Anxiety Disorder (GAD)</u>
    a. Benzodiazepine anxiolytics
    b. SSRI antidepressant (i.e., paroxetine)
    c. Venlafaxine
    d. Tricyclic antidepressants (e.g., imipramine)
    e. Buspirone
    f. Benzodiazepine/SSRI antidepressant combination
    g. Hydroxyzine

2. <u>Panic Disorder</u>
    a. Benzodiazepine anxiolytics (acute therapy).
    b. SSRI antidepressants
    c. Tricyclic antidepressants

d. MAOIs
e. Venlafaxine
f. Nefazadone

3. Social Anxiety Disorder (SAD)
    a. Benzodiazepine anxiolytics
    b. SSRI antidepressants (i.e., paroxetine, sertraline)
    c. Venlafaxine
    d. MAOIs
    e. Beta-blockers

4. Obsessive-Compulsive Disorder (OCD)
    a. SSRI antidepressant (i.e., fluoxetine sertraline, paroxetine, fluvoxamine)
    b. Clomipramine (tricyclic antidepressant)

5. Posttraumatic Stress Disorder (PTSD)
    a. SSRI antidepressant (i.e., sertraline, paroxetine)
    b. Nefazodone
    c. MAOIs
    d. Buspirone

IX. RECOMMENDATIONS

No brand name antianxiety agent offers any significant clinical advantage in general use over the drugs, strengths, and dosage forms of multisource anxiolytics listed in Table I.

Brand name, single entity antianxiety agents can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multisource (generic) formulation. The price competitive point will be determined by Alabama Medicaid.

Thus, no brand name antianxiety agents are recommended to the P&T Committee for preferred drug status.

APPENDIX A

DSM-IV-TR DIAGNOSTIC CRITERIA FOR …….

- Generalized Anxiety Disorders (GAD)
- Panic Attack
- Social Anxiety Disorder (SAD)
- Obsessive-Compulsive Disorder (OCD)
- Posttraumatic Stress Disorder (PTSD)

DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder[1,5]

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The person finds it difficult to control worry.
C. Anxiety and worry, associated with three (or more) of the following six symptoms (with at least some symptoms present more days than not for the past 6 months):
    1. Restlessness or feeling keyed up or on edge
    2. Being easily fatigued
    3. Difficulty concentrating or mind going blank
    4. Irritability
    5. Muscle tension
    6. Sleep disturbance
D. Anxiety and worry, not confined to features of another psychiatric illness (e.g., having a panic attack, being embarrassed in public).
E. Constant worry causing significant distress, and significant impairment in social, occupational, or other important areas of functioning.
F. Excessive anxiety and worry, not caused by a drug substance (e.g., drugs of abuse or medications), or a general medical disorder, and not occurring exclusively as part of another psychiatric disorder (e.g., mood disorder).

Note:
- The essential feature of generalized anxiety disorder (GAD) is unrealistic or excessive anxiety and worry about a number of events or activities.
- GAD has a gradual onset. Onset typically begins in childhood or adolescence.
- The course of GAD is chronic with periods of remission.
- The majority of GAD patients will develop another mental disorder.

DSM-IV-TR Diagnostic Criteria for Panic Attack[1,5]

A discrete period of intense fear or discomfort, in which at least four of the following symptoms developed abruptly and reached a peak within 10 minutes:
1. Palpitations or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Derealization or depersonalization
10. Fear of losing control or going crazy
11. Fear of dying
12. Numbness or tingling sensations (paresthesias)
13. Chills or hot flushes

Note:
- Panic disorder begins as a series of unexpected (spontaneous) intense, terrifying fear.
- Patients frequently describe symptoms as an overwhelming sense of doom, fear of death, fear of losing control and numerous physical symptoms.[5]
- Panic attack rarely last more than 20 to 30 minutes.
- Many patients experience agoraphobia secondary to a panic attack.
- Panic disorder can induce a significant degree of social and occupational impairment.
- Depression may develop in association with a panic disorder.

DSM-IV-TR Diagnostic Criteria for Social Anxiety Disorder[1,5]

A. Marked, persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.
B. Exposure to the feared social situation provokes anxiety, which may take the form of a situationally bound or predisposed panic attack.
C. The person recognizes that the fear is excessive or unreasonable.
D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.
E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning or social activities or relationships, or there is marked distress about having the phobia.
F. In individuals under 18 years of age, the duration is at least six months.
G. Fear or avoidance is not caused by a drug substance (e.g., drugs of abuse or medication), or a general medical disorder, and not occurring exclusively as part of another psychiatric disorder (e.g., panic disorder).

Note:

- Social anxiety disorder (SAD) is characterized by intense, irrational embarrassment and/or persistent fear of being negatively evaluated or scrutinized in a social or performance situation (e.g., pubic speaking).
- Blushing is the principal physical symptom. Other symptoms include sweating, trembling and speech difficulty.
- The typical age of onset is the midteens.
- Symptoms many persist for 6 months or longer.
- The majority of SAD patients have a comorbid depressive, anxiety or substance abuse disorder.

DSM-IV-TR Diagnostic Criteria for Obsessive-Compulsive Disorder[1,5]

A. Either obsession or compulsions:
   Obsessions as defined by (1), (2), (3), and (4):
   1. Recurrent and persistent thoughts, impulses, or image that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.
   2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.
   3. Attempts are made to ignore or suppress the thoughts, impulses, or images or to eliminate them.
   4. It is recognized that the obsessional thoughts, impulses, or images are a product of the person's own mind (not imposed from without).

   Compulsions as defined by (1) and (2):
   1. Repetitive behaviors (e.g., and washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to certain rules.
   2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to eliminate or they are clearly excessive.
B. The person has recognized that the obsessions or compulsions are excessive or unreasonable.*
C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.
D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder).
E. The disturbance is not due to the direct physiologic effects of a substance or a general medical condition.

*Does not apply to children.

Note:

- If OCD is untreated, it can produce significant work, school and social disability.
- OCD is considered a chronic disorder that will occur throughout adult life for most patients.
- Depression and/or anxiety often coexist with OCD.
- Approximately 50% of patients with OCD have another major mental disorder (e.g., major depression, alcohol or drug abuse, panic disorder, schizophrenia).
- OCD patients properly treated commonly require treatment of a comorbid psychiatric disorder.

DSM-IV-TR Diagnostic Criteria for Posttraumatic Stress Disorder[1,5]

A. Exposure to a traumatic event in which both of the following were present.
   1. The person experienced, witnessed or was confronted with an event(s) that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
   2. The person's response involved intense fear, helplessness, or horror.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1. Recurrent and intrusive distressing recollections of the event (e.g., images, thoughts, or perceptions)
   2. Recurrent distressing dreams of the event
   3. Acting or feeling as if the traumatic event were recurring (e.g., a sense of reliving the experience, illusions, hallucinations, dissociative flashbacks)
   4. Physiologic reactivity on exposure to internal/external cues that symbolize an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness as indicated by at least three of the following:
   1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
   3. Inability to recall an important aspect of the trauma
   4. Diminished interest or participation in significant activities
   5. Feeling of detachment or estrangement from others
   6. Restricted range of affect
   7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage)

D. Persistent symptoms of increased arousal, as indicted by at least two of the following:
   1. Difficulty falling or staying asleep
   2. Irritability or outbursts of anger
   3. Difficulty concentrating
   4. Hypervigilance
   5. Exaggerated startle response

E. Duration of the disturbance (symptoms in criteria B, C., and D) is more than one month.
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note:
- PTSD is a chronic, recurring condition highly associated with suicidal behavior.
- Most persons with PTSD meet criteria for another mental disorder.

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PHARMACOTHERAPY REVIEW
SEDATIVE-HYPNOTICS

I. INTRODUCTION

A. Definition of Primary insomnia: [1]

The Diagnostic and Statistical Manual of Mental Disorders uses the following criteria to define primary insomnia:

- The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder or Parasomnia.
- The disturbance does not occur exclusively during the course of another mental disorder (e.g., Major Depressive Disorder, Generalized Anxiety Disorder, a delirium).
- The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

B. Etiology of Insomnia:[2]

Insomnia is attributable to various etiologies:

- Situational: Work or financial stress; Interpersonal conflicts; Major life events; Jet lag or Shift work.
- Medical: Cardiovascular (angina, arrhythmias, heart failure); Respiratory (asthma, sleep apnea); Chronic pain; Endocrine disorders (diabetes, hyperthyroidism); Gastrointestinal (gastroesophageal reflux, ulcers); Neurologic (delirium, epilepsy, Parkinson's disease); Pregnancy.
- Psychiatric: Mood disorders (depression, mania); Anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorder, panic disorder); Substance abuse (alcohol or sedative-hypnotic withdrawal).
- Pharmacologically Induced: Anticonvulsants; Central adrenergic blockers; Diuretics; Selective serotonin reuptake inhibitors; Steroids; Stimulants.

C. Incidence:

The incidence of insomnia has been consistent for more than 20 years. Between 30 and 35% of adult Americans actually report

insomnia that would warrant drug therapy and 10 to 17% of those suffering from insomnia believe it is serious or chronic. In the elderly population, one-half of those patients over the age of 65 complain of insomnia.[3] Approximately 5% of affected individuals seek medical assistance and 10% to 20% of sufferers use nonprescription drugs or alcohol to facilitate falling to sleep.

D. Management of Insomnia:

Hypnotic drugs produce drowsiness and facilitate the onset of a state that resembles normal sleep in its electroencephalographic characteristics.[4] Ideal sedative-hypnotic medications should bring on sleep within 30 minutes and maintain a normal sleep pattern.[5] Management of insomnia is most effective when the choice of treatment is patient-specific. The patient's age and duration, severity and etiology of insomnia should be considered. Diagnosis and treatment of the underlying cause (e.g., depression, psychosis) may resolve insomnia. For many patients, treatment of insomnia with non-pharmacological behavioral changes may be as effective as drug therapy.[6]

Sedative-hypnotic drugs can be classified by their duration of action (see Figure 2). A medication with a short to intermediate duration of action is recommended for transient insomnia caused by disruption of circadian rhythms (i.e., jet lag, shift work) .[5] Short acting drugs are ideal for the elderly and for those who wish to avoid daytime sedation. Long-acting sedative hypnotics are useful for insomnia involving early morning awakening or insomnia associated with daytime anxiety.[5]

Quickly restoring normal sleep patterns within a few days to weeks may decrease the likelihood of adverse drug effects, development of tolerance and psychological dependence. Administering the lowest effective dose, intermittent dosing (2 to 4 times per week) and short-term therapy can potentially limit negative effects associated with sedative-hypnotic drugs. Drug regimens should be gradually discontinued and the subsequent development of rebound insomnia should be monitored.[7]

This review addresses the following sedative-hypnotic medications approved by the FDA to treat insomnia.

Barbiturate Sedative-Hypnotic Agents		
Phenobarbital*	Mephobarbital*	Amobarbital*
Butabarbital*	Secobarbital*	Pentobarbital*
Tuinal (amobarbital and secobarbital)*		
Miscellaneous Sedative-Hypnotic Agents		
Acetylcarbomal*	Chloral hydrate*	Ethchlorvynol*
Glutethamide*	Paraldehyde*	
Benzodiazepine Non-Selective GABA Agonists		
ProSom (estazolam)*	Doral (quazepam)	Halcion (triazolam)*
Dalmane (flurazepam)*	Restoril (temazepam)*	
Non-Benzodiazepine Selective GABA Agonists		
Ambien (zolpidem)	Sonata (zaleplon)	

* Indicates generic version is available. All multisource products are automatically exempted from any prior authorization requirement.

II. PATHOPHYSIOLOGY AND MECHANISM OF ACTION

A. Mechanism of Action of Treatment Modalities:[4,8]

The barbiturates and benzodiazepines achieve their hypnotic effect by potentiating gamma amino-butyric acid (GABA), a potent inhibitory neurotransmitter in the CNS. GABA's inhibitory effect is mediated by a GABAergic receptor comprised of ligand-gated chloride ion channels.[4] The receptors responsible for producing sedative-hypnotic effects on the chloride ion channel are the $GABA_A$ and gamma-benzodiazepine receptors (types I and II). Barbiturates bind to $GABA_A$ receptors and benzodiazepines bind non-specifically to gamma-benzodiazepine receptors. Zolpidem and zaleplon bind specifically to type I receptors only. Activation of the GABAergic receptor results in an influx of chloride ions diffusing into the cell resulting in a hyperpolarized state, thus inhibiting transmission of a neuronal signal.[4] Barbiturates cause an increase in the duration of chloride channel opening and benzodiazepines cause an increase in the frequency of chloride channel opening.[4, 8]

Gamma-benzodiazepine agonists act as sedative-hypnotics by activation of specific benzodiazepine receptors that facilitate GABAergic transmission and only effect physiologically active receptors. Barbiturates, on the other hand, facilitate transmission by acting on locations more directly associated with the chloride ion channel and produce a non-specific effect on all GABAergic receptors. Low doses of barbiturates act pharmacologically similar to benzodiazepines, but higher doses may cause a significant and even fatal suppression of brain synaptic transmission.[8]

B. Pathophysiology of Sleep:[3]

Sedative-hypnotics affect certain parameters of sleep architecture (see Figure 1). A common effect of all sedative-hypnotic drugs is a reduction of sleep latency, which is a reduction in the time until falling asleep. Other parameters are affected uniquely according to their pharmacological class. A night of sleep cycles through 4 stages and a period of rapid eye movement (REM) sleep. Stages 1 to 4 last approximately 45 minutes and then repeat in reverse order up to stage 2. Subsequently, the first REM cycle transpires for approximately 5 to 7 minutes. The cycles repeat 4 to 6 times throughout a full night of sleep and REM sleep gets progressively longer in the later cycles. As REM sleep increases during the second half of the night, stages 2 and 3 sleep decline and oscillations between stage 4 and REM sleep continue.[4, 9]

Stage 1 is the state of rest between being asleep and awake. It is characterized by a high frequency electroencephalogram (EEG) reading and an easily arousable state of sleep.[10] Stage 1 sleep could occur later in the sleep cycle only when awakened (for any reason). Stages 2 and 3 sleep occur during the first half of the sleep cycle and are characterized by high frequency EEG readings referred to as sleep spindles and K-complexes.[10] Stage 4, also called delta or slow-wave sleep, is characterized by low frequency EEG readings and is the stage of sleep in which vivid nightmares can occur. REM sleep emits a low voltage and mixed frequency reading on an EEG. It is the stage in which restorative sleep is believed to occur.[4, 10]

Figure 1

Effects of Sedative-Hypnotic Drugs on Sleep Parameters[3]

Drug	Sleep Latency	Total Sleep Time	Delta Sleep %	REM Sleep %
Barbiturates	↓	↑	↓	↓
Benzodiazepines	↓	↑	↓	↓
Chloral hydrate	↓	↓	↔	↔
Zaleplon	↓	↑ or ↔	↑	↓
Zolpidem	↓	↑	↑	↔

[3]Wagner j, et. al., 1998.

C. Pharmacokinetics:

Selected pharmacokinetic properties of non-barbiturate sedative-hypnotic drugs are presented below: [7, 9, 11-14]

Figure 2

Selected Pharmacokinetic Properties of Non-Barbiturate Sedative-Hypnotic Drugs						
Drug (generic)	**Adult Dose (mg)**	**Geriatric Dose (mg)**	**Onset of Action (min)**	**Duration of Action**	**Half – Life (hr)**	**Active Metabolite**
First Generation Hypnotic Preparations						
Chloral Hydrate	500-2000	500-2000	30-60	Short	7-10	Yes
Ethchlorvynol	500	nd*	30	Intermediate	10-20	No
Glutethamide	200-500	nd*	nd*	Intermediate-Long	10-12	Yes
Paraldehyde	10-30 (ml)	nd*	10-15	Long	3.4-9.8	Yes
Benzodiazepine Hypnotics						
ProSom (estazolam)	1-2	0.5-1	15-30	Intermediate	10-24	No
Dalmane (flurazepam)	15-30	15	60-120	Long	50-100	Yes
Doral (quazepam)	7.5-15	7.5	20-45	Long	25-41	Yes
Restoril (temazepam)	15-30	7.5-15	45-60	Intermediate	10-17	No
Halcion (triazolam)	0.125-0.25	0.125	15-30	Short	1.5-5.5	No
Non-Benzodiazepine GABA Agonists						
Ambien (zolpidem)	5-10	5	30	Short	2.5	No
Sonata (zaleplon)	10-20	5	15-30	Short	0.9-1.1	No

* nd= no data available

III. Barbiturate and Non-Benzodiazepine, Non-Selective GABA Agonist Sedative-Hypnotic Compounds[4,15-16]

The barbiturate and non-benzodiazepine, non-selective GABA agonists are effective sedative-hypnotic drugs. They decrease sleep latency and maintain sleep by non-selectively binding to GABAergic receptors in the brain causing an increase in the chloride ion concentration in the neuron (see: II. Mechanism of action) and affecting the transmission of a neuronal signal.[4] Chronic administration can induce rapid pharmacokinetic tolerance, even at low doses.

The barbiturate and miscellaneous non-selective agents have a narrow therapeutic index. Excessive dosing can lead to acute intoxication, respiratory depression and hypotension.[15] **Physical dependence and subsequent withdrawal symptoms along with significant drug interactions and unfavorable side effect profile make the barbiturates and miscellaneous non-selective GABA agonists a poor choice for the treatment of insomnia and offer no clinical advantage over benzodiazepines and selective GABA agonists**.[15]

IV. BENZODIAZEPINE AND SELECTIVE GABA AGONIST SEDATIVE-HYPNOTIC COMPOUNDS

A. Benzodiazepines approved by the FDA to treat insomnia:

A low capacity to produce fatal CNS depression has resulted in benzodiazepines overtaking barbiturates and miscellaneous non-selective GABA agonists as agents of choice to treat insomnia.[4] Benzodiazepines bind with high affinity to the gamma-benzodiazepine region on GABAergic receptors in the brain, thereby allosterically enhancing the post-synaptic inhibition of GABA.[4] Benzodiazepines decrease sleep latency, decrease the number of awakenings during sleep, increase time spent in stage 2 sleep and decrease time spent in stage 3, stage 4 and REM sleep (see: II. B. Sleep Parameters).[4] Consequently, benzodiazepines can reduce nightmares taking place during stage 4. Restorative sleep is believed to be achieved during REM sleep, owing to the "well-rested" feeling after awakening. Although reducing the time spent in REM sleep should theoretically have a negative effect on sleep efficiency, it is not yet supported by clinical data.[3] The decreased amount of time spent in REM sleep can be offset by an increased frequency of REM sleep late in the sleep cycle[4] and can therefore be minimal if a full night of sleep is achieved. The benzodiazepines' alteration of sleep architecture has not affected subjective feelings of restful sleep in published clinical trials.[17-19]

B. Ambien® (zolpidem):

Zolpidem is an imidazopyridine sedative-hypnotic with a chemical structure unrelated to that of the benzodiazepines, with which they share similar pharmacologic actions.[9, 20] Zolpidem selectively binds to the gamma-benzodiazepine-1 receptor on the GABAergic receptor complex. As a result, zolpidem produces minimal anxiolytic activity and no muscle relaxant or anticonvulsant activity at the recommended dose.[4] Both zolpidem and benzodiazepines decrease sleep latency and produce almost identical changes in sleep EEG's.[20] However, zolpidem increases the length of time spent in delta or stage 4 sleep and produces minimal or no change in the duration of

REM sleep.[3] Zolpidem is an effective agent for the treatment of transient short-term or chronic insomnia and it has fewer medication-related interactions than the benzodiazepines which is advantageous in the elderly population.[5] It can also be safely administered concurrently with SSRI's to treat insomnia commonly experienced during depression.[5] These advantages may prove to be useful in the treatment of insomnia, but because zolpidem works at the GABA receptor complex, it theoretically carries the same risks as benzodiazepines, including dependence, and use beyond 4 weeks is not recommended.[7]

C. Sonata® (zaleplon):

Zaleplon, a short-acting, selective gamma-benzodiazepine-1 receptor agonist, is another effective compound to initiate the onset of sleep. However, selected pharmacokinetic properties (see: II. C. Pharmacokinetic Properties), including short half-life and duration of action may limit its effectiveness in facilitating the maintenance of a full night of sleep.[9] Zaleplon's short half-life can reduce the occurrence of residual drowsiness upon awakening and its adverse effects appear to be dose-dependent.[9] Administration of the lowest sedative hypnotic dose can minimize the occurrence of common side effects (e.g., dizziness, headache and drowsiness) .[13]

Metabolism of zaleplon involves the cytochrome P450 (CYP450) enzyme pathway. Therefore, special caution should be taken in polypharmaceutical drug regimens, especially those containing Tagamet® (cimetidine). Cimetidine can increase serum blood levels of zaleplon up to 85% higher than baseline.[20] Zaleplon has proven efficacy to decrease sleep latency, and possesses a low side effect profile, but its high incidence of drug interactions with CYP3A4 and short duration of action may limit its usefulness in a sedative-hypnotic drug regimen.

V. INDICATIONS[11-13]

Figure 3

Indications of Benzodiazepine and Selective GABA Agonists[11-13]	
Drug	**Indication**
Estazolam Flurazepam Quazepam Temazepam Triazolam	Insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings or early morning awakening. Can be used for recurring insomnia or poor sleeping habits and in acute or chronic medical situations requiring restful sleep.
Zolpidem Zaleplon	Short-term treatment of insomnia

[11-13]Facts and Comparisons, Clinisphere. July, 2003

VI. ADVERSE EFFECTS

A. Benzodiazepines:[11]

Many of the CNS depressant effects may potentially be avoided when used as directed to facilitate a full night's sleep of 6 to 8 hours. Some of the *most frequently occurring adverse effects* are daytime sedation, memory and psychomotor impairment, tolerance, withdrawal reactions, and rebound insomnia.[5]

Selected other adverse effects by system to the benzodiazepine sedative-hypnotic class as a whole are included below:

Cardiovascular: Palpitations; chest pains; tachycardia; hypotension

CNS: Headache; nervousness; talkativeness; apprehension; irritability; confusion; euphoria; relaxed feeling; weakness; tremor; lack of concentration; coordination disorders; confusional states/memory impairment; depression; dreaming/nightmares; insomnia; paresthesia; restlessness; tiredness; dysesthesia. Dizziness, drowsiness, lightheadedness, staggering, ataxia, falling, particularly in elderly or debilitated patients.

Dermatologic: Dermatitis/allergy; sweating, flushes, pruritus, skin rash (rare).

Gastrointestinal: Heartburn; nausea; vomiting; diarrhea; constipation; GI pain; anorexia; taste alterations; dry mouth; excessive salivation (rare); death from hepatic failure in a patient also receiving diuretics; jaundice; glossitis.

Lab test abnormalities: Elevated AST, ALT, total and direct bilirubin and alkaline phosphatase with flurazepam.

Miscellaneous: Body/joint pain; tinnitus; GU complaints; cramps/pain; congestion. Leukopenia, granulocytopenia, blurred vision, burning eyes, faintness, difficulty in focusing, visual disturbances, shortness of breath, apnea, and slurred speech (rare).

B. Non-benzodiazepines:

Ambien® (zolpidem):[12]

The most frequently occurring adverse effects associated with Ambien® include headache, drowsiness, myalgia, nausea, dizziness, daytime sedation, memory disturbance, nightmares, confusion, depression, hangover effects, falls and asthenia. Other adverse effects listed below have occurred during clinical trials at a rate of 0.1% to 1% or greater.[5, 21]

Cardiovascular: Cerebrovascular disorder, hypertension, tachycardia
CNS: Ataxia, confusion, euphoria, insomnia, vertigo, stupor, tremor
Autonomic nervous system: Increased sweating, pallor, postural hypotension
Gastrointestinal: Constipation, dysphagia, flatulence, gastroenteritis, hiccup
Genitourinary: Cystitis, urinary incontinence
Reproductive: Menstrual disorder, vaginitis
Hepatic: Increased ALT
Metabolic/Nutritional: Hyperglycemia
Musculoskeletal: Arthritis
Respiratory: Bronchitis, coughing, dyspnea
Special senses: Diplopia, vision abnormal; eye irritation/pain, scleritis, taste perversion, tinnitus
Miscellaneous: Asthenia, edema, falling, fever, malaise, menstrual disorder, vaginitis

Sonata® (zaleplon):[13]

The most frequently occurring adverse effects associated with Sonata® include headache, myalgia, dizziness, nausea, somnolence, asthenia, and abdominal pain. Zaleplon's adverse effects are dose related and utilizing the lowest possible dose to achieve sleep should be used. Other adverse effects listed below have occurred during clinical trials at a rate of 0.1% to 1% or greater.[5, 21]

Cardiovascular: Migraine
CNS: Depression, hypertonia, nervousness, thinking abnormal (mainly difficulty concentrating)
Dermatological: Pruritus, rash
Gastrointestinal: Constipation, dry mouth
Musculoskeletal: Arthritis
Respiratory: Bronchitis
Special senses: Conjunctivitis
Miscellaneous: Back pain, chest pain

VII. CONTRAINDICATIONS[5,11-13]

In general, sedative-hypnotic drugs should be avoided in patients with a *potential for addiction, alcohol abuse, chronic obstructive lung disease, sleep apnea, depression and during the performance of hazardous tasks requiring alertness*. Benzodiazepines and zaleplon should be avoided during *pregnancy and lactation*. The use of zolpidem *during pregnancy* should be considered *only if the benefits outweigh the risks*. There are no well controlled studies to support their safety.

VIII. DRUG INTERACTIONS[22-24]

The following are considered to be clinically significant drug interactions. The level of severity is ranked on a scale from 1 to 5. A level of 1 is a severe and well documented interaction and a level of 5 is being of no more than unlikely or having only possible documentation of occurrence and/ or clinical significance. *The drug interactions falling in the 1 to 3 range are considered clinically significant* and will be presented in the following table:

Figure 4

Benzodiazepine Drug Interactions		
Precipitant Drug **(Significance Level)**	**Object Drug* (mechanism of interaction)**	
Azole anti-fungal agent (**2**)	BZ (inhibition of CYP3A4 metabolism)	↑
Benzodiazepines (**3**)	Digoxin (unknown mech.)	
Benzodiazepines (**3**)	Neuromuscular Blockers (non-depolarizing agents)	↔
Benzodiazepines (**3**)	Phenytoin (alteration of metabolism)	↑
Cimetadine (**3**)	BZ (metabolized by oxidation)	
Diltiazem (**2**)	BZ (decreased metabolism and first pass of triazolam)	
Disulfram (**3**)	BZ (inhibits hepatic oxidation)	
Ethanol/ CNS Depressants (**3**)	BZ (synergistic effects)	
Fluvoxamine (**3**)	BZ (decreased clearance)	
Indinivir (**2**)	BZ (inhibition of CYP 3A4 metabolism)	
Isoniazid (**3**)	BZ (metabolized by oxidation)	
Macrolides (**2**)	Triazolam (decreased metabolism)	
Nefazodone (**3**)	BZ (inhibition of CYP 3A4 metabolism)	
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI's) (**2**)	BZ (inhibition of CYP 3A4 metabolism)	
Omeprazole (**3**)	BZ (decreased oxidative metabolism)	
Oral Contraceptives (**3**)	BZ (increased hepatic metabolism)	↓
Probenecid (**3**)	BZ (inhibits conjugation in the liver)	↑
Rifampin (**2**)	BZ (increased oxidative metabolism)	↓
Ritonavir (**2**)	BZ (inhibition of hepatic metabolism)	↑
Smoking (**3**)	BZ	↓
Theophyllines (**3**)	BZ (competitive binding to intracerebral receptors)	↓

* ↑Object drug increased ↓Object drug decreased
Adapted with permission from Drug Interaction Facts, July 2003

Ambien® (zolpidem):
Like the benzodiazepine hypnotics, drugs that effect CYP3A4 metabolism may have a significant interaction with Ambien®.

Figure 5

Ambien ® (zolpidem) Drug Interactions		
Precipitant Drug	**Object Drug***	
Azole anti-fungal agents (**3**)	Zolpidem	↑
Ritonavir (**2**)		↑
SSRI's (**3**)		↑
Rifampin (**3**)		↓

* ↑= Object drug increased ↓= Object drug decreased
Adapted with permission from Drug Interaction Facts, July, 2003

Sonata® (zaleplon):
The CYP3A4 enzyme is modestly involved in zaleplon metabolism. Theoretically, high doses of drugs which inhibit or induce this enzyme may increase or decrease the effects of zaleplon, but no clinical evidence is yet available to support this claim.

IX. SUMMARY

Trials have been conducted to compare the safety, efficacy and tolerability of the sedative-hypnotics in the hope of finding one agent to be superior to all of the others. Triazolam (0.25 mg), temazepam (15 mg and 30 mg) and zolpidem (10 mg) offer effective improvement of selected sleep parameters (see II. B. Sleep Parameters) .[3, 17-19] The occurrence of side effects has been comparable between triazolam and zolpidem.[17-19, 25] Tolerability and rebound insomnia are also comparable between triazolam and zolpidem.[26] Zaleplon is an equally effective agent to decrease sleep latency, but due to its shorter duration of action, it may not provide the maintenance of a full night of sleep. Interactions with drugs metabolized by the CYP450 enzymes can also limit zaleplon's usefulness as a sleep-inducing agent in patients taking multiple medications. Temazepam is not metabolized by CYP450 enzymes and has no active metabolites. If temazepam is taken before bedtime, it too, can be effective in treating transient episodes of insomnia and produce a full night of sleep.[9]

An evidence-based review of the clinical literature shows that when used properly with the expectation of a standard 6-8 hour night of sleep, [5, 27] no brand name product should be preferred over any generically available benzodiazepine GABA agonist. Issues concerning the benzodiazepines decreasing the percentage of time spent in REM sleep have not been proven to be clinically significant and the

decrease is considered to be minimal because of the increase in the number of cycles of REM sleep in the later hours of sleep.[3, 4] The table below lists the two multisource benzodiazepine hypnotics with the highest degree of documented safety and efficacy. These agents provide prescribers with effective choices for managing insomnia of all etiologies.

Figure 6

Selected Multi-Source Agents to Manage Insomnia			
Drug	**Strength (mg)**	**Dosage Form**	**Duration of Action[7]**
Triazolam	0.125*, 0.25	Tablets	Short
Temazepam	15*, 30	Capsules	Intermediate

* elderly dose

X. RECOMMENDATIONS

A review of available clinical studies and the evidence does not support the contention that any brand name benzodiazepine or non-benzodiazepine GABA agonist is of greater efficacy, safety, or tolerability than triazolam or temazepam. Zaleplon and zolpidem may be useful in certain patient populations, but their use for general treatment of insomnia shows no significant clinical advantage over triazolam or temazepam. Access to zaleplon, zolpidem, barbiturate and miscellaneous non-barbiturate sedative-hypnotics should be guided by the prior authorization process of Alabama Medicaid.

Brand name sedative-hypnotics can be considered for preferred status if the net cost of the brand name agent is competitive with a pharmaceutically and/or therapeutically equivalent multisource sedative-hypnotic formulation. The price competitive point will be determined by Alabama Medicaid.

No brand name sedative-hypnotic agents are recommended to the P&T Committee for preferred drug status.

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PHARMACOTHERAPY REVIEW
Anti-Hypertensive Agents

1. Classes Discussed in this Review:

Diuretics
Alpha-Adrenergic Receptor Antagonists
Central Alpha-Adrenergic Agonists
Direct Vasodilators
Peripheral Adrenergic Neuron Antagonists
Beta-Receptor Antagonists
Calcium Channel Antagonists
ACE Inhibitors
Angiotensin-II Receptor Antagonists (ARB)
Combination Products

A. Diuretics

1. Products:

A. Thiazides: The following table displays the available thiazide diuretics.

Generic Name	Brand Name	Generic Available
Chlorothiazide	Diuril	Yes
Chlorthalidone	Thalitone	Yes
Hydrochlorothiazide	HydroDIURIL	Yes
Hydroflumethiazide	Diucardin	No
Indapamide	Lozol	Yes
Methyclothiazide	Enduron Aquatensen	No Yes
Metolazone	Zaroxolyn Mykrox	No No
Polythiazide	Renese	No
Trichlormethiazide	Naqua	Yes

B. Loop Diuretics: The following table displays the available loop diuretics.

Generic Name	Brand Name	Generic Available
Bumetanide	Bumex	Yes
Ethacrynic acid	Edecrin	No
Furosemide	Lasix	Yes
Torsemide	Demadex	Yes

C. Potassium-Sparing Diuretics: The following table displays the available potassium-sparing diuretics.

Generic Name	Brand Name	Generic Available
Amiloride	Midamor	Yes
Eplerenone	Inspra	No
Spironolactone	Aldactone	Yes
Triamterene	Dyrenium	No

D. Diuretic Combinations: The following table displays the available diuretic combination products.

Generic Name	Brand Name	Generic Available
Amiloride + HCTZ	Moduretic	Yes
Spironolactone + HCTZ	Aldactazide	*
Triamterene + HCTZ	Dyazide / Maxzide	Yes

HCTZ = hydrochlorothiazide * Generic for 25/25 mg; no generic 50 mg/50 mg formulation

2. Hypertension Guidelines Statements: The following statements are from various hypertension guidelines addressing the use of diuretics to treat hypertension.

JNC VII:[1] Thiazide diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another antihypertensive agent (e.g., ACE-inhibitors, ARBs, beta-blocker, and calcium channel blockers). A diuretic also is preferred in patients with compelling indications (heart failure [HF], high coronary disease risk, diabetes, recurrent stroke prevention). Aldosterone antagonists with loop diuretics are recommended in patients with HF; aldosterone antagonists are preferred also in patients as post-MI care. Increased doses of loop diuretics may be needed in patients with chronic renal disease.

WHO/ISH:[2] Thiazide diuretics are indicated for the treatment of hypertension in patients with isolated systolic hypertension, HF, and diabetes. Loop diuretics can be prescribed to treat hypertensive patients with HF or renal failure. Potassium-sparing diuretics are useful for hypertensive patients with HF or low potassium levels. Diuretics are one of the most useful medication classes to treat hypertension and can reduce major cardiovascular events.

British Hypertension Society:[3] Low-dose thiazide diuretics are recommended as initial therapy unless a contraindication or compelling indication for another antihypertensive agent exists.

Hypertension in African-Americans:[4] Thiazides are one of the recommended agents for initial hypertension therapy. Thiazides are preferred over the other diuretic subclasses; the other diuretic subclasses are usually reserved for hypertensive patients with other disorders (e.g., renal dysfunction, HF, at risk for hypokalemia).

The Medical Letter Practice Guidelines:[5] Thiazide diuretics are effective in hypertensive patients with impaired renal function. Loop diuretics are indicated for hypertensive patients with renal insufficiency; loop diuretics may be less effective as antihypertensive agents compared to thiazides in patients with normal renal function. Potassium-sparing diuretics are primarily used in combination with other diuretics to prevent or correct hypokalemia.

Athletes/Physically Active Patients Hypertensive Guidelines:[6] Thiazide diuretics are considered second-line therapy in salt sensitive athletes and physically active patients with hypertension. Thiazides are a reasonable choice in patients that exercise only casually, in physically active elderly patients, and in African-American patients. Loop diuretics should not be prescribed to treat hypertension in athletes and other physically active patients (increased side effects). In fact, all diuretics are banned by sports regulatory bodies.

3. General Comments:

- Thiazide diuretics enhance the antihypertensive efficacy of multidrug regimens, can be useful when used alone in achieving blood pressure (BP) control, and are more affordable than other hypertensive agents.[1,4-6]
- Thiazides are the preferred diuretic to treat hypertension. Loop diuretics are primarily prescribed to patients with reduced renal function and/or intolerance to thiazides. Loop diuretics cause a more intense immediate diuresis than thiazides and may require greater than once daily dosing. Potassium-sparing diuretics are not commonly prescribed as monotherapy due to a lesser

antihypertensive effect than the other diuretics. Potassium-sparing diuretics are usually combined with other antihypertensive agents (e.g., thiazide).[1,4,5]

- The majority of the outcome studies evaluating a diuretic to reduce adverse events (e.g., stroke, HF, mortality) include HCTZ or chlorthalidone. For instance, the ALLHAT study evaluated chlorthalidone against amlodipine and lisinopril. Although there was no difference between the three groups in the primary endpoint (fatal CHD, non-fatal MI), patients randomized to receive chlorthalidone had a lower incidence of selected secondary endpoints (e.g., HF) than patients randomized to receive the other two agents.[7]
- Results of The Second Australian National Blood Pressure Study (ANBP2) reported ACE inhibitors were better than diuretics to reduce the composite of death from any cause or any cardiovascular event (e.g., MI, HF, stroke, TIA).[8] However, this study was specifically conducted in elderly patients (65-84 years of age) with an absence of recent cardiovascular events (endpoint: 22.83% vs. 24.22%, respectively [HR = 0.89; 95% CI, 0.79-1.00; p = 0.05]).
- The literature does not consider one thiazide to be clinically superior or more toxic than another, as long as equivalent doses are prescribed.[9-12]
- Ethacrynic acid (via the oral route) has not been reported to be more effective than the other loop diuretics. In addition, a higher incidence of GI side effects can occur with ethacrynic acid compared to the other loop diuretics. Ethacrynic acid may be prescribed to patients who experienced a severe allergic reaction to sulfonamides.[9,11]

4. Eplerenone

- Eplerenone is a new potassium-sparing diuretic that has recently been marketed.
- Pharmacology: Competitive aldosterone receptor antagonist[13,14]
- Indication: Treat hypertension (either as monotherapy or in combination)[15]
- Clinical Studies:
  - Hypertension: Eplerenone has been evaluated in patients with hypertension.[16-20]
    - Eplerenone decreases SBP and DBP in a dose-dependent fashion, as do other diuretics, in patients with mild-to-moderate hypertension.
    - In patients with systolic hypertension (≥ 50 years of age; n = 269), eplerenone lowered mean SBP similar to amlodipine (-21 vs -20 mmHg) after 24 weeks; mean DBP was also lowered (-5 vs. -7 mmHg, respectively; p = 0.014).[17]
    - Eplerenone was reported to be no different than amlodipine in reducing untreated systolic hypertension (SBP 140-190 mmHg). Patients > 50 years were randomized to non-blinded eplerenone 50 mg/day (n = 134) or amlodipine 2.5 mg/day (n = 135). The dose was increased to 200 mg/day and 10 mg/day at week 24 in 65% and 56%, respectively. Mean SBP was reduced by 20 mmHg in both groups; DBP was reduced by -4.5 and -6.9 mmHg, respectively. This study was not designed to measure reductions in adverse events (e.g., MI, stroke).
  - Heart failure: Eplerenone has been evaluated in patients with HF, although not yet FDA-approved for this indication.[21-23]
- Safety:
  - Contraindications: Patients with serum potassium >5.5 mEq/L; type 2 diabetes plus microalbuminuria; serum creatinine >2 mg/dL (males) or >1.8 mg/dL (females); creatinine clearance <50 mL/min; concomitant therapy that includes potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene) or strong inhibitors of CYP450 3A4 (e.g., ketoconazole, itraconazole).[15]

- Warning: As with the other potassium-sparing diuretics, eplerenone may induce hyperkalemia.[15]
- Drug Interactions: Eprelenone is metabolized by the CYP450 3A4 enzyme system. Besides the medications listed in the contraindications, increases in eplerenone Cmax and AUC occur with other medications that inhibit this isoenzyme (e.g., erythromycin, verapamil). The risk of hyperkalemia is increased by combining eplerenone with ACE inhibitors or ARBs.[14,15]

- Dosing: The starting dose is 50 mg once daily; the dose may be increased to 50 mg BID. The dose should not exceed 100 mg/day due to increased risk for hyperkalemia. No dosage adjustments are needed with the elderly or patients with hepatic dysfunction.[15]
- Therapeutic Use: This agent has not been directly compared to other potassium-sparing diuretics, nor extensively documented to be clinically superior to other antihypertensive diuretics.

5. **Recommendation for Diuretic Review:** More similarities than differences in efficacy, safety and dosing are present among the diuretic sub-classes. No brand name diuretic agent offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) diuretics listed in section 1 above. No brand name diuretics are recommended to the P&T Committee for preferred drug status. Brand name single entity diuretics can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

6. **References:** On file.

B. Alpha-Adrenergic Receptor Antagonists (Alpha-Blockers)

1. **Products:** The following table displays the available alpha-blockers.

Generic Name	Brand Name	Generic Available
Doxazosin	Cardura	Yes
Prazosin	Minipress	Yes
Terazosin	Hytrin	Yes

2. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of alpha-adrenergic receptor antagonists to treat hypertension.

JNC VII:[1] Alpha blockers are not recommended as initial therapy or as preferred agents in patients with compelling indications. Alpha-blockers may increase the chance of reducing standing SBP by ≥ 10 mmHg plus cause dizziness or fainting. This medication class has a potential favorable effect in men with prostatism.

WHO/ISH:[2] Postural hypotension is a concern.

British Hypertension Society:[3] Not preferred as initial agents to treat hypertension. May be an appropriate choice for type 2 diabetics, men with prostatism or in African-Americans (in combination).

Hypertension in African-Americans:[4] Alpha-blockers should not be used as first-line agents.

The Medical Letter Practice Guidelines:[5] Associated with various side effects (e.g., HF with doxazosin); useful for men with prostatism.

Athletes/Physically Active Patients Hypertensive Guidelines:[6] Cause no major changes in energy metabolism during exercise; no major effects on training or sports performance.

3. **General Comments:**
    - According to the above guidelines, the alpha-adrenergic receptor antagonists are not considered as initial therapy in hypertension management.
    - The ALLHAT study included a group of patients randomized to doxazosin. However, this therapy was stopped before the conclusion of the trail due to an increase in HF with this medication.[7]
    - These agents are most commonly prescribed as add-on therapy to control blood pressure in patients with other disease states (e.g., men with prostatism).[1,3,5]
    - The first dose of all agents of this class should be taken at bedtime (due to first-dose effect).[5]

4. **Dosing:** The following table displays the usual dosing regimen for the alpha-blockers.

Agent	Brand Name	Daily Dose	Frequency
Doxazosin	Cardura	1 - 16 mg	Once daily
Prazosin	Minipress	1 - 20 mg	BID-TID
Terazosin	Hytrin	1 - 20 mg	Once daily

5. **Recommendation for Alpha-Adrenergic Receptor Antagonists Review:** No literature is available which documents that brand name alpha-adrenergic receptor antagonists are more effective and/or safer than multi-source agents of this medication class. No brand name alpha-adrenergic receptor antagonist offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) alpha-adrenergic receptor antagonists listed in section 1 above. No brand name alpha-adrenergic receptor antagonists are recommended to the P&T Committee for preferred drug status. Brand name single entity alpha-adrenergic receptor antagonists can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

6. **References:** On file.

C. Central Alpha-Adrenergic Agonists

1. **Products:** The following table displays the available central alpha-adrenergic agonists.

Generic Name	Brand Name	Generic Available
Clonidine	Catapres	Yes
Clonidine (transdermal)	Catapres TTS	No
Guanabenz	Wytensin	Yes
Guanfacine	Tenex	Yes
Methyldopa	Aldomet	Yes

2. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of the central alpha-adrenergic agonists to treat hypertension.
    JNC VII:[1] Central alpha blockers are not recommended as initial therapy or as preferred agents in patients with hypertension. Methyldopa is a preferred agent to treat hypertension in pregnant women.
    WHO/ISH:[2] Side effects caused by these drugs are more significant than other more commonly prescribed agents (e.g., ACE inhibitors, beta-blockers). Methyldopa has a well-documented and continued role in treating pregnant women with hypertension.

British Hypertension Society:[3] Not recommended as initial therapy for hypertensive patients. Methyldopa is considered drug-of-choice for idiopathic hypertension in pregnancy or pre-eclampsia.

Hypertension in African-Americans:[4] Centrally acting agents are not recommended for initial monotherapy due to annoying side effects.

The Medical Letter Practice Guidelines:[5] This antihypertensive class frequently causes sedation, dry mouth, and impotence.

Athletes/Physically Active Patients Hypertensive Guidelines:[6] Have no major effects on training or sports performance. However, these agents are not normally prescribed due to side effects.

3. **General Comments:**
   - According to the above hypertensive guidelines, the central alpha-adrenergic agonists are not considered as initial therapy.
   - Current literature does not consider these agents as first-line therapy due to a higher incidence of side effects than newer antihypertensive agents.[7,8]

4. **Dosing:** The following table displays the usual dosing regimen for the central alpha-adrenergic agonists.

Agent	Brand Name	Daily Dose	Frequency
Clonidine	Catapres	0.1 - 0.6 mg	BID-TID
Clonidine (transdermal)	Catapres TTS	0.1 - 0.3 mg/day	Apply one patch weekly
Guanabenz	Wytensin	4 - 64 mg	BID
Guanfacine	Tenex	1 - 3 mg	Once daily
Methyldopa	Aldomet	250 - 2000 mg	BID

5. **Recommendation for Alpha-Adrenergic Agonists Review:** No literature is available that documents the brand name central alpha-adrenergic agonists are more effective and/or safer than multi-source agents of this medication class. In addition, this antihypertensive class is not considered as initial therapy since these agents have more side effects than other agents used to lower blood pressure. No brand name central alpha-adrenergic agonist offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) alpha-adrenergic agonists listed in section 1 above. No brand name central alpha-adrenergic agonists are recommended to the P&T Committee for preferred drug status. Brand name single entity central alpha-adrenergic agonists can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

6. **References:** On file.

D. Direct Vasodilators:

1. **Products:** The following table displays the available direct vasodilators.

Generic Name	Brand Name	Generic Available
Hydralazine	Apresoline	Yes
Minoxidil	Loniten	Yes

2. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of direct vasodilators to treat hypertension.

JNC VII:[1] Hydralazine and minoxidil are not recommended as initial therapy or as preferred agents in patients with hypertension.

WHO/ISH:[2] The side effects prevent these drugs from being first-line antihypertensive agents.

British Hypertension Society:[3] Not recommended as initial therapy. Hydralazine may be used as a second-line agent for hypertension during pregnancy.

Hypertension in African-Americans:[4] Direct vasodilators are not recommended for initial monotherapy due to annoying side effects.

The Medical Letter Practice Guidelines:[5] Reflex tachycardia is a frequent side effect with these agents. These agents should not be administered as monotherapy, but with a beta-blocker or a centrally-acting drug to minimize the reflex increase in heart rate and cardiac output. Minoxidil should be reserved for severe hypertension refractory to other therapies.

Athletes/Physically Active Patients Hypertensive Guidelines:[6] Not addressed in document.

3. **General Comments:**
   - The direct vasodilators are not considered initial antihypertensive therapy.
   - Current literature does not consider these agents as first-line due to being associated with a higher incidence of side effects than newer antihypertensive agents.[7,8]
   - The direct vasodilators are most commonly prescribed as add-on therapy to control blood pressure in only selected patient types.

4. **Dosing:** The following table displays the usual dosing regimen for the direct vasodilators.

Agent	Brand Name	Daily Dose	Frequency
Hydralazine	Apresoline	40 - 200 mg	BID-QID
Minoxidil	Loniten	2.5 - 40 mg	Once to twice daily

5. **Recommendation for Direct Vasodilators Review:** No literature is available which documents that brand name direct vasodilators are more effective and/or safer than multi-source agents of this medication class. In addition, this antihypertensive class is not considered as initial therapy since these agents have considerably more side effects than other agents used to lower blood pressure. No brand name direct vasodilator offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) vasodilators listed in section 1 above. No brand name direct vasodilators are recommended to the P&T Committee for preferred drug status. Brand name single entity direct vasodilators can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

6. **References:** On file.

E. Peripheral Adrenergic Neuron Antagonists:

1. Products: The following table displays the available peripheral adrenergic neuron antagonists.

Generic Name	Brand Name	Generic Available
Guanadrel	Hylorel	No longer on market
Guanethidine	Ismelin	No longer on market
Reserpine	Serpasil	Yes

2. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of peripheral adrenergic neuron antagonists to treat hypertension.
   - JNC VII:[1] Peripheral adrenergic neuron antagonists are not recommended as initial therapy or as preferred agents in patients with hypertension.
   - WHO/ISH:[2] Side effects from these drugs are less favorable than other more commonly prescribed agents (e.g., ACE inhibitors, beta-blockers).
   - British Hypertension Society:[3] Not addressed in this document.
   - Hypertension in African-Americans:[4] This medication class not addressed.
   - The Medical Letter Practice Guidelines:[5] These agents are associated with bothersome side effects (e.g., depression with high dose reserpine; cardiac output reduction with guanadrel).
   - Athletes/Physically Active Patients Hypertensive Guidelines:[6] Not addressed in document.

3. **General Comments:**
   - According to the above guidelines, the peripheral adrenergic neuron antagonists should not be considered for initial antihypertensive therapy.
   - Current literature does not consider these agents as first-line therapy due to a higher incidence of side effects than newer antihypertensive agents.[7,8]
   - The peripheral adrenergic neuron antagonists might be prescribed as add-on therapy to control blood pressure in selected patient types in rare instances.

4. **Dosing:** The following table displays the usual dosing regimen for the peripheral adrenergic neuron antagonists.

Agent	Brand Name	Daily Dose	Frequency
Guanadrel	Hylorel	10 - 75 mg	BID
Reserpine	Reserpine	0.05 - 0.1 mg	Once daily

5. **Recommendation for Peripheral Adrenergic Neuron Antagonists Review:** No literature is available that supports the brand name peripheral adrenergic neuron antagonists as more effective and/or safer than multi-source agents of this medication class. In addition, this antihypertensive class is not considered as initial therapy since these agents have considerably more side effects than other agents used to lower blood pressure. No brand name peripheral adrenergic neuron antagonist offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) peripheral adrenergic neuron antagonists listed in section 1 above. No brand name peripheral adrenergic neuron antagonists are recommended to the P&T Committee for preferred drug status. Brand name single entity peripheral adrenergic neuron antagonists can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

6. **References:** On file.

F. Beta-Adrenergic Receptor Antagonists (Beta-Blockers)

1. Products: The following table displays the available beta-blockers.

Generic Name	Brand Name	Generic Available
Atenolol	Tenormin	Yes
Betaxolol	Kerlone	Yes
Bisoprolol	Zebeta	Yes
Metoprolol- immediate release Metoprolol- extended release	Lopressor Toprol XL	Yes No
Nadolol	Corgard	Yes
Propranolol- immediate release Propranolol- extended release	Inderal Inderal-LA	Yes Yes

Generic Name	Brand Name	Generic Available
Timolol	Blocadren	Yes
Intrinsic Sympathomimetic Activity		
Acebutolol	Sectral	Yes
Carteolol	Cartrol	No
Penbutolol	Levatol	No
Pindolol	Visken	Yes
Alpha-Blocking Activity		
Carvedilol	Coreg	No
Labetalol	Normodyne / Trandate	Yes

2. Pharmacology: Compete with beta-adrenergic receptor agonists that leads to: slowing of sinus heart rate; depressed AV conduction; decreased cardiac output; and reduction of SBP/DBP (sitting, standing, and during exercise).[1]

3. Indications: The following table displays the FDA-approved indications for the beta-receptor antagonists.

Generic Name	Hypertension	Other
Atenolol[2]	X	Angina pectoris due to coronary atherosclerosis; post-MI (hemodynamically stable)
Betaxolol[3]	X	-
Bisoprolol[4]	X	-
Metoprolol-immediate release[5]	X	Angina pectoris; post-MI (hemodynamically stable)
Metoprolol-extended release[6]	X	Angina pectoris; heart failure (NYHA class II or III of ischemic, hypertensive, or cardiomyopathic origin)
Nadolol[7]	X	Angina pectoris
Propranolol-immediate release[8]	X	Angina pectoris due to coronary atherosclerosis; cardiac arrhythmias (SVT's, VT's, etc); post-MI (clinically stable); migraine prophylaxis; essential tremor; hypertrophic subaortic stenosis; pheochromocytoma (adjunctive)
Propranolol-extended release[9]	X	Angina pectoris due to coronary atherosclerosis; migraine prophylaxis; hypertrophic subaortic stenosis
Timolol[10]	X	Post-MI (clinically stable); migraine prophylaxis
Intrinsic Sympathomimetic Activity		

Acebutolol[11]	X	Ventricular arrhythmias
Carteolol[12]	X	-
Penbutolol[13]	X	-
Pindolol[14]	X	-
Alpha-Blocking Activity		
Carvedilol[15]	X	Mild to severe heart failure of ischemic or cardiomyopathic origin; left ventricular dysfunction (ejection fraction ≤ 40%) following MI in stable patients
Labetalol[16]	X	-

X= FDA approved indication

4. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of beta-receptor antagonists to treat hypertension.
   - JNC VII:[17] Agents can be combined with diuretics in managing hypertension. Lower response in African-Americans.
   - WHO/ISH:[18] Compelling indications are: CHD; HF; tachyarrhythmia; or migraine headache.
   - British Hypertension Society:[19] Useful in managing hypertension with coexisting MI; and angina. Suitable agents for use in type 1 diabetes and diabetic nephropathy. Labetalol is used as second-line agent for hypertension in pregnancy. May be ineffective as monotherapy in African-American patients.
   - Hypertension in African-Americans:[20] As monotherapy, do not lower blood pressure as well as in Caucasian patients. This is not a reason to avoid this class in this patient type. Effective in combination with a diuretic or ACE inhibitor.
   - The Medical Letter Practice Guidelines:[21] Effective agents, but may be less effective in African-American patients. As monotherapy, less effective than diuretic alone for the elderly. Agents with ISA activity may be preferred for individuals developing symptomatic bradycardia or postural hypotension with other agents of this class. Non-ISA acting class agents are generally preferred to treat angina or post-MI.
   - Athletes/Physically Active Patients Hypertensive Guidelines:[22] Beta-receptor antagonists with cardioselectivity are not recommended for athletes and other physically active patients unless underlying conditions (e.g., CAD) require use. US Olympic Committee has banned use of all agents of this class in precision events (e.g., shooting, ice skating, archery, diving).

5. **General Comments:**
   - All of these class agents (when administered at effective doses) cause clinically relevant blood pressure reductions in hypertensive patients.[23-25]
   - The antihypertensive efficacy among the different agents does not show consistent results for a greater advantage of one beta-receptor antagonist versus another.[23-25]
   - Beta-receptor antagonists are one of the antihypertensive classes that have been documented to reduce morbidity and mortality from heart failure and other comorbid cardiovascular conditions.[17,21,23,26-51]
   - Contraindications to the beta-receptor antagonists include sinus bradycardia, greater than first degree heart block, and cardiogenic shock; the agents with ß2 activity should be cautiously prescribed in patients with asthma.[1]
   - Side effect profile is primarily dependent upon the subclass. ß1-selective agents (at normal daily doses) are associated with the lowest incidence of side effects compared to the other class agents.[1]

6. Dosing: The following table displays the common dosing regimens for the beta-receptor antagonists.

Generic Name	Brand Name	Daily Dose	Frequency
Atenolol	Tenormin	25 – 100 mg	Once daily – BID
Betaxolol	Kerlone	5 – 40 mg	Once daily
Bisoprolol	Zebeta	5 – 20 mg	Once daily
Metoprolol- immediate release Metoprolol- extended release	Lopressor Toprol-XL	50 – 200 mg 25-200 mg	Once daily – BID Once daily
Nadolol	Corgard	20-320 mg	Once daily
Propranolol- immediate release Propranolol- extended release	Inderal Inderal LA	40 – 200 mg 60 – 240 mg	BID - QID Once daily
Timolol	Blocadren	10 – 60 mg	BID
Intrinsic Sympathomimetic Activity			
Acebutolol	Sectral	200 – 1200 mg	Once daily – BID
Carteolol	Cartrol	2.5 – 10 mg	Once daily
Penbutolol	Levatol	20 mg	Once daily
Pindolol	Visken	10 – 60 mg	BID
Alpha-Blocking Activity			
Carvedilol	Coreg	12.5 – 50 mg	BID
Labetalol	Normodyne Trandate	200 – 1200 mg	BID

7. Safety:

The primary adverse effects that occur with beta-blocker therapy include bradycardia, hypotension, fatigue, dizziness, diarrhea, upper respiratory tract infection and chest pain. Episodes of syncope have been reported with carvedilol use, which is possibly due to α-1 receptor blockade.[49-51]

The MERIT-HF trial reported a greater mean decrease in heart rate with metoprolol than placebo (14 vs 3 beats per minute, respectively). Systolic blood pressure was decreased more with metoprolol than placebo (-2.1 vs 3.5 mmHg; $p = 0.013$); there was no difference in change of diastolic blood pressure (-2.6 vs 2.3 mmHg; $p > 0.05$).[44] Dizziness, bradycardia, and hypotension were the most common side effects that were reported from the use of metoprolol.[45]

8. Recommendation for Beta-Receptor Antagonist Review: No literature is available that documents the brand name beta-receptor antagonists are more effective and/or safe than multi-source agents of this medication class to treat hypertension. No brand name beta-receptor antagonist offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) beta-receptor antagonists listed in section 1 above to treat hypertension. No brand name beta-receptor antagonist is recommended to the P&T Committee for preferred drug status. Brand name single entity beta-receptor antagonists can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

11. References: On file

G. Calcium Channel Blockers (CCB's):

1. **Products:** The following table displays the available calcium channel blockers (CCBs).

Generic Name	Brand Name Examples	Generic Available
Non-Dihydropyridine		
Verapamil – immediate release	Calan Verelan	Yes Yes
Verapamil – extended release	Calan SR Isoptin SR	Yes Yes
Verapamil – controlled onset-extended release	Covera-HS Verelan-PM	No No
Diltiazem – immediate release	Cardizem	Yes
Diltiazem – extended release	Cardizem CD Cartia XT	Yes Yes
Dihydropyridine		
Amlodipine	Norvasc	No
Felodipine	Plendil	No
Isradipine – immediate release	DynaCirc	No
Isradipine – extended release	DynaCirc CR	No
Nicardipine – immediate release	Cardene	Yes
Nicardipine – extended release	Cardene SR	No
Nifedipine – immediate release	Adalat Procardia	Yes Yes
Nifedipine – extended release	Adalat CC Procardia XL	Yes Yes
Nisoldipine	Sular	No

2. **Calcium Channel Antagonist Classification:** Calcium channel blockers (CCBs) are composed of three chemical classes (diphenylalkylamines, benzothiazepines, and dihydropyridines).[1,2] The dihydropyridines (amlodipine, felodipine, isradipine, nifedipine, nicardipine, nimodipine and nisoldipine) possess the greatest selectivity for vascular smooth muscle and these agents cause greater peripheral arterial dilation than other CCBs. An exception to this is nimodipine, which dilates cerebral arterioles rather than peripheral blood vessels; this agent is used primarily in the treatment of subarachnoid hemorrhage.[1,2]

   The two other CCB classes, diphenylalkylamines (verapamil) and benzothiazepines (diltiazem), depress sinus node automaticity, prolong AV nodal conduction time, increase the refractory period of the AV node, depress myocardial contractility, reduce peripheral vascular resistance, and prevent coronary artery spasm. Although both of these agents possess cardiac and vascular actions, verapamil controls AV nodal conduction to a better degree than diltiazem and therefore is considered the CCB of choice to treat patients with supraventricular tachycardia.[1,2]

   One additional CCB, bepridil, is more selective for the coronary rather than the peripheral vasculature. This agent is useful for the treatment of stable angina pectoris, however, due to the adverse effect profile, bepridil is reserved for refractory patients unable to be treated with other agents.[1,2]

3. Indications: The following table displays the FDA-approved indications for the CCBs.

Generic Name	Hypertension	Chronic Stable Angina	Other
Non-Dihydropyridine			
Verapamil – extended release[3,4]	X		
Verapamil – controlled onset-extended release	X[5,6]	X[5]	
Diltiazem – extended release*[7]	X	X	Vasospastic angina
Dihydropyridine			
Amlodipine[8]	X	X	Vasospastic angina
Felodipine[9]	X		
Isradipine[10] – extended release	X		
Nicardipine[11] – extended release	X	X	
Nifedipine[12] – immediate release	X		
Nifedipine– extended release	X[13,14]	X[14]	Vasospastic angina[14]
Nisoldipine[15]	X		

* Many extended-release diltiazem preparations are marketed (e.g., Cardizem LA, Tiazac, Diltia XT). Not all of these formulations have all three of these FDA-approved indications.

4. CCB Pharmacokinetics: The following table displays selected pharmacokinetic properties of the dihydropyridine CCBs.

Agent	Protein Binding	Onset	Peak Time (hours)	Bioavailability (%)	Half-Life (hours)	Duration of Action (hrs)
Amlodipine[8] (Norvasc)	93%	30 - 50 mins	6 - 12	64 - 90	30 - 50	24
Felodipine[9] (Plendil)	> 99%	2 - 5 hrs	16 - 24	20	11 – 16	16 - 24
Isradipine[10] (Dynacirc CR)	95%	n/a	8 - 10	15 - 24	8	8 - 16
Nicardipine[11] (Cardene SR)	> 95%	1 - 2 hrs	2 - 6	35	2 - 4	2 - 6
Nifedipine[13] (Adalat CC)	92-98%	20 mins	2.5 - 5 & 6 - 12	84 - 89	7	24
Nifedipine[14] (Procardia XL)	92-98%	20 mins	6	86	2 (IR)	24
Nisoldipine[15] (Sular)	> 99%	n/a	6 - 12	5	7 - 12	> 24

5. **Dihydropyridine CCBs:** The following table displays selected drug-drug and drug food interactions.

Agent	Grapefruit Juice	Fatty Meals	Food	Drug Interactions	Metabolism
Amlodipine[8] (Norvasc)	Slight increase in AUC			diltiazem	Hepatic
Felodipine[9] (Plendil)	Bioavailability incr by 2 times	Increases Cmax by 60%		CYP 450 3A4 inhibitors, Anticonvulsants, Itraconazole	Hepatic
Isradipine[10] (Dynacirc CR)			Bioavail decr by 25%	Fentanyl	Hepatic
Nicardipine[11] (Cardene SR)		Cmax decr by 45% AUC decr by 25% Trough incr by 75%		Cimetidine, Fentanyl, Cyclosporin	Hepatic
Nifedipine[13] (Adalat CC)	AUC incr by 2 times, Cmax incr by 2 times	Cpeak incr by 60%, Time to peak incr		Beta-blockers, Cimetidine	Hepatic
Nifedipine[14] (Procardia XL)				Beta-blockers, Cimetidine	Hepatic
Nisoldipine[15] (Sular)	Cmax incr by 3 times AUC incr by 5 times	Cmax incr by 300%; Drug exposure incr by 25%		Cimetidine, CYP 450 inducers, Phenytoin	Hepatic

6. **Dihydropyridine CCB Discussion:** The dihydropyridine CCBs do not have a long serum half-life (except amlodipine). Thus, the dosage unit is formulated to release the drug contents over an extended period of time (i.e., sustained-release, extended-release). The following table displays the delivery systems of these formulations.

Agent	Matrix
Amlodipine[8] (Norvasc)	Inherent long half-life, no special matrix
Felodipine[9] (Plendil)	Extended Release Tablet
Isradipine[10] (Dynacirc CR)	Controlled Release Tablet - Osmotic pump
Nicardipine[11] (Cardene SR)	Sustained Release Capsule - Coated beads
Nifedipine[13] (Adalat CC)	Extended Release Tablet - External coat and internal core contain nifedipine; coat is a slow release formulation and core as fast release formulation.
Nifedipine[14] (Procardia XL)	GI Therapeutic System - Osmotic pump
Nisoldipine[15] (Sular)	Extended Release Tablet - external coat and internal core contain nisoldipine, coat as a slow release formulation and core as fast release formulation.

7. **Hypertension Guidelines Statements:** The following statements are from various hypertension guidelines addressing the use of CCBs to treat hypertension.

   JNC VII:[16] These agents can be combined with diuretics. Long-acting agents are preferred if ischemic heart disease is present. Beneficial in reducing CVD and stroke incidence in patients with diabetes. Effects not diminished as most other antihypertensives in African-Americans. Useful for patients with peripheral arterial disease or Raynaud syndrome or certain arrhythmias.

American Diabetes Association:[17] "Calcium channel blockers appear to be appropriate agents in addition to, but not instead of, ACE inhibitors and beta-blockers. CCBs may reduce coronary events and reduce albumin excretion."

WHO/ISH:[18] Compelling indications for verapamil and diltiazem in addition to hypertension management are tachyarrhythmia; and angina.

British Hypertension Society:[19] Option to treat type 1 diabetes and diabetic nephropathy; appears to be one of the initial choices for hypertension in type 2 diabetes. Can be used as initial therapy for African-Americans; effective also in combination with other antihypertensive agents.

Hypertension in African-Americans:[20] Besides diuretics, considered drug-of-choice as monotherapy to treat hypertension. Most patients not controlled with single drug; add agent from this class to initial therapy. Combination with ACE inhibitors also useful regimen.

The Medical Letter Practice Guidelines:[21] Short acting CCBs should not be used to treat hypertension. The risks of CVD and HF may be increased with calcium channel antagonists compared to ACE inhibitors, beta-blockers and diuretics.

Athletes/Physically Active Patients Hypertensive Guidelines:[22] Are usually well-tolerated and effective. Often prescribed as first-line agents in African-American athletes.

8. Additional Guidelines for Use: The American College of Cardiology/American Heart Association recommends long-acting dihydropyridine or non-dihydropyridine CCBs to relieve angina symptoms. These agents do not increase the risk of cardiac adverse events. However, immediate-release or short-acting dihydropyridine CCBs can increase the risk of cardiac adverse events. Due to the sustained 24-hour effects of long-acting CCBs, these agents are often preferred over long-acting nitrates for maintenance therapy. Calcium channel blockers are recommended over beta-receptor antagonists for patients with selected co-existing disease states (e.g., depression, Raynaud's syndrome). Certain co-existing disease states may warrant selecting a dihydropyridine CCB instead of a non-dihydropyridine CCB. Examples include atrioventricular block, moderate-to-severe left ventricular dysfunction (≤ 40%), aortic insufficiency. In addition, non-dihydropyridine CCBs are recommended to be prescribed instead of a dihydropyridine CCB in selected co-existing disease states (e.g., hypertrophic cardiomyopathy, rapid atrial fibrillation, asthma).[23]

9. Comments:

Calcium channel blockers are effective and relatively well tolerated agents to manage hypertension and/or angina. This medication class is often appropriate for use in hypertensive African-Americans as first line therapy.

Many clinical trials have directly compared dihydropyridine CCBs in patients with hypertension. The primary outcome was a reduction in blood pressure. Results of these trials indicate that on average, dihydropyridine CCBs lower both SBP and DBP to a similar extent. In addition, the side effect profiles between the comparative agents were not extensively different.[24-31]

The CONVINCE trial evaluated the controlled-onset extended-release (COER) verapamil formulation (Covera-HS) to prevent CV adverse events to standard JNC-VI recommended therapy (beta-receptor antagonist or diuretic).[32] The primary endpoint was the composite of MI, nonfatal stroke, or death from CV disease, whichever occurs first. Secondary endpoints included the incidence of primary endpoints occurring between 6 am and noon. Hypertensive patients ≥ 55 years of age with at least one other established risk factor for CV disease (e.g., diabetes, cigarette smoking) were enrolled. Patients were randomized to COER verapamil 180 mg at bedtime (n = 8179) or either atenolol 50 mg or HCTZ 12.5 mg in the morning (n = 8297). The dose was doubled if SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg; selected other antihypertensive agents were

added if SBP and/or DBP did not achieve goal values. Baseline patient demographics were well matched at baseline. Mean age was 65.6 years and 48.7% were between 55-64 years of age; 56% were female and 84% Caucasian. No difference was reported between two groups in the incidence of primary endpoint occurrence (4.5% vs 4.4% in the COER-verapamil vs. other regimen, respectively; p = 0.77; HR = 1.02 [95% CI, 0.88-1.18]). The only secondary endpoint that was different was in death or hospitalization due to bleeding (1.4% vs 1%; p = 0.003). More patients randomized to COER-verapamil experienced first CV disease-related event during time period of 6 am to noon (99 vs 88; HR = 1.15; 95% CI, 0.86-1.53). Median follow-up was 3 years and no difference in SBP/DBP reductions was reported; both regimens reduced mean SBP/DBP by 13.6/7.8 mmHg. The investigators concluded that COER verapamil is not equivalent to atenolol or HCTZ in preventing CV disease-related events.

The ALLHAT trial was conducted to determine the difference between chlorthalidone, amlodipine, and lisinopril in reducing the risk of cardiovascular disease (CVD) in high-risk patients.[33] The primary endpoint was the incidence of fatal CHD and non-fatal MI. Secondary endpoints were: all-cause mortality; fatal and non-fatal stroke; combined CHD measured as the primary endpoint, coronary revascularization, and hospitalized angina; and combined CVD measured as combined CHD, stroke, other treated angina, HF [fatal, hospitalized, or treated non-hospitalized], and peripheral arterial disease. Patients enrolled were $\geq$ 55 years of age with stage 1 or 2 hypertension (HTN) plus one additional risk factor for CHD. Excluded patients included: history of HF and/or left ventricular ejection fraction of < 35%. Participants were randomized to double-blind step 1 therapy: chlorthalidone: 12.5 - 25 mg/day (n = 15,255), amlodipine 2.5 - 10 mg/day (n = 9048), or lisinopril 10 - 40 mg/day (n = 9054). If blood pressure was not controlled, step 2 was initiated (atenolol 25 - 100 mg/day, reserpine 0.05 - 0.2 mg/day or clonidine 0.1 - 0.3 mg BID. Step 3 could be added afterwards (hydralazine 25 - 100 mg BID). All three groups well matched at baseline; mean age was 67 years (42% between age 55-64 years), ~47% were female and ~47% were Caucasian. Baseline mean SBP/DBP was 146 / 84 mmHg; at baseline, 90.2% of patients were receiving anti-hypertensive therapy and ~36% taking ASA daily. Mean duration of follow-up was 4.9 ($\pm$ 1.4) years. No difference between three medications was reported in incidence of primary endpoint occurrence (6-year rate per 100 persons: 11.5, 11.3 and 11.4 for chlorthalidone, amlodipine, and lisinopril). Other results of interest include: percent receiving original study drug (or same class), 80.5%, 80.4%, 72.6% (chlorthalidone, amlodipine, and lisinopril, respectively); percent receiving Step 2 or 3 drug, 40.7%, 39.5%, 43%, respectively; percent achieving blood pressure goal of < 140 / 90 mmHg at 5 years, 68%, 66%, 61%, respectively; reduction in SBP/DBP from baseline was not primary focus of study; >90% of the patients were taking anti-hypertensive therapy at baseline. The investigators concluded that chlorthalidone (i.e., thiazide-diuretics) should be considered as first-line antihypertensive therapy over amlodipine and lisinopril.

10. Dosing: The following table displays the common dosing regimen for the calcium channel blockers.

Generic Name	Brand Name Examples	Daily Dose	Frequency
Non-Dihydropyridine			
Verapamil – immediate release	Calan Verelan	120 – 480	BID - TID
Verapamil – extended release	Calan SR Isoptin SR	120 – 480 mg	Once to twice daily
Verapamil – controlled onset-extended release	Covera-HS Verelan PM	180 – 480 mg 200 – 400 mg	At bedtime
Diltiazem – immediate release	Cardizem	30 – 60 mg	TID - QID

Diltiazem – extended release	Cardizem CD Dilacor XR Tiazac	120 – 360 mg 120 – 480 mg 120 – 540 mg	Once daily
Dihydropyridine			
Amlodipine	Norvasc	2.5 – 10 mg	Once daily
Felodipine	Plendil	2.5 – 10 mg	Once daily
Isradipine – immediate release	DynaCirc	5 – 10 mg	BID
Isradipine – extended release	DynaCirc CR	5 – 10 mg	Once daily
Nicardipine – immediate release	Cardene	60 – 120 mg	TID
Nicardipine – extended release	Cardene SR	60 – 120 mg	BID
Nifedipine – immediate release	Adalat Procardia	10 – 20 mg	TID
Nifedipine – extended release	Adalat CC Procardia XL	30 – 90 mg	Once daily
Nisoldipine	Sular	10 – 60 mg	Once daily

11. Recommendation for Calcium Channel Antagonist Review:
No brand name CCB offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) CCBs listed in section 1 above. No brand name CCBs are recommended to the P&T Committee for preferred drug status. Brand name single entity CCBs can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

12. References: On file

H. Angiotensin Converting Enzyme (ACE) Inhibitors

1. Products: The following table displays the available ACE inhibitors.

Generic Name	Brand Name	Generic Available
Benzapril	Lotensin	No
Captopril	Capoten	Yes
Enalapril	Vasotec	Yes
Fosinopril	Monopril	No
Lisinopril	Prinivil / Zestril	Yes
Moexipril	Univasc	No
Perindopril	Aceon	No
Quinapril	Accupril	No
Ramipril	Altace	No
Trandolapril	Mavik	No

2. Pharmacology: Antagonizes the enzyme that converts angiotensin I to angiotensin II; prevents vasoconstriction.[1,2]

3. Indications: The following table displays the FDA-approved indications for the ACE inhibitors.

Generic Name	Hypertension	Heart Failure	Other
Benzapril[3]	X		-
Captopril[4]	X	X	Left ventricular dysfunction post-MI Diabetic nephropathy in patients with type I insulin dependent diabetes mellitus and retinopathy
Enalapril[5]	X	X	Asymptomatic LV dysfunction
Fosinopril[6]	X	X	-
Lisinopril[7]	X	X	To improve survival after acute MI in hemo- dynamically stable patients
Moexipril[8]	X		-
Perindopril[9]	X		-
Quinapril[10]	X	X	-
Ramipril[11]	X		Heart failure post-MI Reduce risk of MI, stroke, and death from CV causes in patients ≥ 55 years at high risk or developing a major CV event because of a history of CAD, stroke, PVD, or diabetes, accompanied by one other risk factor
Trandolapril[12]	X		Heart failure post-MI Left ventricular dysfunction post-MI

X = FDA approved indication

4. Hypertension Guideline Statements: The following information is taken from the published hypertension guidelines regarding the use of ACE inhibitors to treat this disorder.

JNC VII:[13] Compelling indications are: HR; post-MI; high coronary disease risk; diabetes; chronic kidney disease; recurrent stroke prevention. Can be added to diuretic therapy, which is preferred agent as initial therapy. Combine with beta-receptor antagonist in acute coronary syndromes; also for post-MI therapy. Recommended as agent of choice for HF (asymptomatic or symptomatic). Reduces CVD and stroke in patients with diabetes. Reduces diabetic and nondiabetic renal disease progression; also recurrent stroke in combination with thiazide. Response is lower in African-American patients. Useful in patients with left ventricular hypertrophy or peripheral arterial disease.

American Diabetes Association:[14] “”Because many studies demonstrate the benefits of ACE inhibits on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as first-line agent in most patients with diabetes is reasonable. In patients with microalbuminemia or clinical nephropathy, ACE inhibitors (type 1 and type 2 patients) are considered first-line therapy for the prevention of and progression of nephropathy.” ACE inhibitors are recommended for all patients with microalbuminuria or advanced stages of nephropathy. “The effect of ACE inhibitors appears to be a class effect.”

WHO/ISH:[15] Compelling indications are: HR; HF; CHD; diabetic nephropathy.

British Hypertension Society:[16] Compelling indication: HR; HF; left ventricular dysfunction; type 1 diabetic nephropathy. ACE inhibitors reduce the rate of renal function decline (i.e., renoprotective) in patients with type 1 diabetes. ACE inhibitors are considered options in patients with type 2 diabetes. May not be effective as monotherapy in African-American patients; but good in combination with diuretics, calcium channel antagonists or alpha-blockers.

Hypertension in African-Americans:[17] As monotherapy, does not lower blood pressure as well as in Caucasian patients. This is not a reason to avoid this class of antihypertensive in this patient type. Patients with compelling indications (e.g., renal disease, HF, diabetic nephropathy, left ventricular dysfunction with or without diabetes) for an agent of this class should not be denied the medication. Effective in combination with a diuretic, calcium channel antagonist or beta-receptor antagonist.

The Medical Letter Practice Guidelines:[18] Effective in lowering blood pressure but less effective in African-American patients (unless combined with thiazide). Risk of adverse events (e.g., death) reduced in patients with HF or left ventricular dysfunction post-MI; also preserves renal function in type 1 diabetics. May preserve renal function in patients with non-diabetic nephropathies.

Athletes/Physically Active Patients Hypertensive Guidelines:[19] Agents of first choice, especially individuals with diabetes. Not associated with any deleterious effects on training or competition. Recommend an adequate cool-down period to avoid postural hypotension after intense exercise.

5. **Heart Failure Guidelines:** The following information is taken from the American Heart Association / American College of Cardiology guidelines regarding the use of ACE inhibitors.
   - "ACE inhibitors should be preferred over the use of angiotensin II receptor antagonists or direct-acting vasodilators (e.g., a combination of hydralazine and isosorbide dinitrate)."[20]
   - "Although most of the evidence supporting an effect of ACE inhibitors on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival. Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE-inhibiting agents are superior to other ACE inhibitors in any clinical aspect of HF. Nevertheless, in selecting among ACE inhibitors, it is recommended to give preference to ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (e.g., captopril, enalapril, Lisinopril) because these studies have clearly defined a dose that is effective in modifying the natural history of the disease."[20]

6. **General Comments:**
   - All ACE inhibitors (when administered at effective doses) produce clinically relevant blood pressure reductions in hypertensive patients that is significantly greater than placebo.[21,22]
   - However, the efficacy (and safety) among the different ACE inhibitors does not show consistent results for a greater advantage of one ACE inhibitor versus another (provided effective doses are administered).[21,23]
   - As monotherapy, ACE inhibitors have a reduced blood pressure lowering effect and higher incidence of angioedema in African-Americans compared to non-African-Americans.[17]
   - Adverse effects of ACE inhibitors include cough, hyperkalemia, angioedema, metallic taste, rash, shortness of breath, fatigue, orthostatic hypotension and agranulocytosis (captopril).[18,21-24]

- Cough is associated with all ACE inhibitors and data stating which agent may have the lowest frequency are conflicting.[23]
- Except for captopril, all ACE inhibitors can be initially dosed once daily.
- The ALLHAT study evaluated lisinopril against chlorthalidone and amlodipine. Although there was no difference between the three groups in the primary endpoint (fatal CHD, non-fatal MI), patients randomized to receive chlorthalidone had a lower incidence of selected secondary endpoints (e.g., HF) than patients randomized to receive the other two agents.[26]
- Results of The Second Australian National Blood Pressure Study (ANBP2) reported ACE inhibitors (i.e., enalapril) were better than diuretics (i.e., HCTZ) to reduce the composite of death from any cause or any cardiovascular event (e.g., MI, HF, stroke, TIA). However this study was specifically conducted in elderly (65-84 years of age) with absence of recent cardiovascular events (endpoint: 22.83% vs. 24.22%, respectively [HR = 0.89; 95% CI, 0.79-1.00; p = 0.05]). In addition at the end of the study, only 58% and 62% of the patient were receiving assigned therapy with ACE inhibitor or diuretic, respectively.[27]
- The HOPE study concluded ramipril reduced death, MI and stroke in a variety of high-risk patients without a low ejection fraction or HF. Patients were at least 55 years of age and had to have a history of CAD, stroke, diabetes or peripheral vascular disease plus one other risk factor (e.g., hypertension, cigarette smoking). Approximately 52% of the randomized patients had a history of MI, but only 39.5% and 76% were taking a beta-receptor antagonist and antiplatelet therapy, respectively. Less the 30% (28.6%) were taking lipid-lowering therapy (specific cholesterol values provided; 65.9% had a documented elevated total cholesterol level).[28]
- Interestingly, the HOPE study has been used as an example to critique primary literature. Two publications discussing the analysis of combined endpoints included the HOPE study as an example. The authors of these two articles illustrated less-than-desired approaches to data presentation and analysis methods by using results presented in the HOPE study.[29,30]
- The MICRO-HOPE study analyzed the HOPE trial results in a specific subgroup. A total of 3577 (37.5%) people enrolled in the HOPE study were diagnosed with diabetes. The incidence of the combined primary endpoint was lower with ramipril than placebo (15.3% vs. 19.8%; p = 0.004, RRR = 25% [95% CI, 12-36]). All three individual components of the primary endpoint (MI, stroke, cardiovascular death) were lower with ramipril also. Many of the other secondary endpoints were statistically better with ramipril; for instance, overall nephropathy rate was reduced with ramipril v. placebo (6.5% vs. 8.4%; p = 0.027, RRR = 24%).[31]
- Another analysis of the HOPE trial reported ramipril reduces the risk of developing diabetes. A total of 5720 (61.5%) patients without diabetes at baseline were included in this subgroup. Diabetes, recorded via self-reports, was reported in less patients randomized to ramipril than placebo (3.6% vs. 5.4%, p < 0.001; RR = 0.66 [95% CI, 0.51-0.85]). The investigators do state that the development of diabetes was not a primary or secondary endpoint. Thus these study results require confirmation via a large prospective trial designed to evaluate this issue.[32]
- The results of the African-American Study of Kidney Disease and Hypertension (AASK) reported ACE inhibitors appear to be more effective than beta-receptor antagonist (e.g., metoprolol) or dihydropyridine calcium channel antagonist (e.g., amlodipine) in slowing glomerular filtration rate. Patients with hypertension with renal disease were enrolled and followed for 3-6.4 years.[33]
- Various other studies have evaluated an ACE inhibitor to reduce adverse events. An outline of these selected studies is presented in the table at the end of this review.[28,34-37]

7. **Dosing:** The following table displays the common dosage regimens for the ACE inhibitors.

Generic Name	Brand Name	Daily Dose	Frequency
Benazepril	Lotensin	10 – 80 mg	Once to twice daily
Captopril	Capoten	12.5 – 150 mg	BID - TID
Enalapril	Vasotec	2.5 – 40 mg	Once to twice daily
Fosinopril	Monopril	10 – 80 mg	Once to twice daily
Lisinopril	Prinivil / Zestril	5 – 40 mg	Once daily
Moexipril	Univasc	7.5 – 30 mg	Once to twice daily
Perindopril	Aceon	4 – 8 mg	Once to twice daily
Quinapril	Accupril	5 – 80 mg	Once to twice daily
Ramipril	Altace	1.25 – 20 mg	Once to twice daily
Trandolapril	Mavik	1 – 8 mg	Once to twice daily

8. **Comments:** The ACE inhibitors are efficacious agents to lower blood pressure and are associated with a low incidence of adverse effects compared to most other antihypertensive agents. All of the ACE inhibitors lower blood pressure to a similar extent. Excluding captopril, the side effect profile of these agents is indistinguishable. Cough is the most common side effect of the ACE inhibitors and the incidence is similar among the ACE inhibitors. Many guidelines recommend an ACE inhibitor as initial therapy for patients with hypertension and coexisting disease. For instance, the JNC-7 recognizes six disease states as compelling indications for specific drug classes; ACE inhibitors are recommended as an initial therapeutic option for all six disease states. Data have been published documenting a reduction in the risk of adverse events (e.g., stroke, MI) with selected ACE inhibitors compared to either another antihypertensive agent or placebo. The majority of studies using another antihypertensive agent as the comparative agent documented a greater reduction in adverse event risk with the ACE inhibitor, regardless of which specific ACE inhibitor was selected. Some practitioners have considered the actions of the ACE inhibitors to be a class effect. In fact, the American Diabetes Association guidelines state “the effect of ACE inhibitors appears to be a class effect”. The multi-source ACE inhibitors (captopril, enalapril, lisinopril) have been extensively researched in regards to reducing morbidity and mortality.

10. **Recommendations for the Angiotensin Converting Enzyme (ACE) Inhibitors:** No brand name ACE inhibitor offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) ACE inhibitors listed in section 1 above. No brand name ACE inhibitor is recommended to the P&T Committee for preferred drug status. Brand name single entity ACE inhibitors can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price “competitive” point will be determined by AL Medicaid.

11. **Reference:** On file

I. Angiotensin-II Receptor Antagonists

1. Products: The following table displays the marketed angiotensin receptor antagonists (ARBs).

Generic Name	Brand Name	Generic Formulation
Candesartan	Atacand	No
Eprosartan	Teveten	No
Irbesartan	Avapro	No
Losartan	Cozaar	No
Olmesartan	Benicar	No
Telmisartan	Micardis	No
Valsartan	Diovan	No

2. Pharmacology: Antagonizes the angiotensin II receptor; prevents vasoconstriction.[1,2]

3. Indications: The following table displays the FDA-approved indications for the ARBs.

Generic Name	Hypertension	Other
Candesartan[3]	X	-
Eprosartan[4]	X	-
Irbesartan[5]	X	Hypertension with type 2 diabetes and diabetic nephropathy
Losartan[6]	X	Hypertension with: Left ventricular hypertrophy (to reduce stroke); Nephropathy in Type 2 diabetic patients
Olmesartan[7]	X	-
Telmisartan[8]	X	-
Valsartan[9]	X	Patients with heart failure (NYHA class II-IV) that are intolerant to ACE inhibitors

X = FDA approved indication

4. Hypertension Guideline Statements: The following information is taken from the published hypertension guidelines regarding the use of ARBs to treat this disorder.

JNC VII:[10] One of the therapy options for patients with symptomatic ventricular dysfunction or end-stage heart disease, diabetic hypertension, and chronic kidney disease; only place ARBs are differentiated is in reducing progression to macroalbuminuria in diabetic hypertension.

American Diabetes Association:[11] ""Because many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as first-line agent in most patients with diabetes is reasonable. In patients with microalbuminemia or clinical nephropathy, ACE inhibitors (type 1 and type 2 diabetic patients) are considered first-line therapy for the prevention of and progression of nephropathy."

WHO/ISH:[12] Compelling indications are: HF; diabetic nephropathy.

British Hypertension Society:[13] The only compelling indication is for patients with ACE inhibitor-induced cough. Possible indications are in patients with heart failure or intolerance of other antihypertensive agents.

Hypertension in African-Americans:[14] One of the options to treat hypertension in combination with other antihypertensive agents. As monotherapy, do not lower blood pressure to the same extent as in Caucasian patients. "May be considered as effective as an ACE inhibitor in the treatment of all patients with diabetic nephropathy who have higher than goal blood pressure." Adding an ARB may

be as beneficial as an ACE inhibitor in patients with HF. Do not recommend combination of ARB, ACE inhibitor plus beta-blocker.

The Medical Letter Practice Guidelines:[15] Effective in lowering blood pressure without causing cough. "Whether ARBs provide the same cardiac and renal protections as ACE inhibitors remains to be established."

Athletes/Physically Active Patients Hypertensive Guidelines:[16] Generally recommended only for patients who cannot tolerate ACE inhibitors.

5. **Hypertension Efficacy:**[17-35] Various published studies compare one ARB to another ARB. Few studies compare an ARB to ACE inhibitors or another commonly prescribed antihypertensive agent. According to the results of studies evaluating the ARBs, these agents are efficacious in lowering blood pressure. The majority of studies report no significant therapeutic differences between the ARBs.

ARB versus ACE Inhibitors

The following table presents some of the published studies comparing an ARB to an ACE inhibitor. The results of these studies indicate ARBs at appropriate doses lower mean SBP and/or DBP to a similar extent as ACE inhibitors either as monotherapy or as part of an antihypertensive multi-drug regimen. Although a few studies report statistical difference, the number of these studies is less in number than studies reporting no differences between the two medication classes. Various elements of experimental design should be considered when studies are reviewed that include, but are not limited to, study duration, dose titration and/or additional medications being added, non-equivalent doses being compared, and mean reduction in SBP and/or DBP values being reported.

ARB	ACE Inhibitor	Duration (weeks)	Mean Reduction in SBP/DBP (mmHg)
Losartan 50 mg QD[36]	Enalapril 20 mg	12	-10.6/8.4 vs. -12.9/10.6
Losartan 50 mg QD Losartan 100 mg QD[37]	Enalapril 20 mg QD	8 12	DBP: -10.1 vs. -9.9 vs. -11.2 DBP: -13 vs. -8.9 vs. -14.7 p<0.05
Losartan 50 mg QD +/- HCTZ 12.5 mg[38]	Enalapril 5-10 mg QD +/- HCTZ 25 mg	12	DBP: -10.3 vs. -9.8
Candesartan 12 mg QD[39]	Enalapril 10 mg QD	12	DBP: -10 vs. -10.6
Candesartan 8-16 mg QD	Enalapril 10-20 mg QD	8	-13.5/8.7 vs. -9.9/5.8 (p< 0.05)
Candesartan 8-16 mg QD	Enalapril 10-20 mg QD	12	-19/11 vs. -13/9 (p < 0.05)
Candesartan 4-8 mg QD	Enalapril 10-20 mg QD	8	-12.5/10 vs. -14/10
Telmisartan 20-80 mg QD[30] +/- HCTZ 12.5-25 mg	Enalapril 5-20 mg QD +/- HCTZ 12.5-25 mg	26	-22.1/12.8 vs -20.1/11.4
Telmisartan 40 mg QD Telmisartan 80 mg QD	Enalapril 20 mg QD	4	-10/7.9 vs. -15.5/8.7 vs. -10.2/9.6
Telmisartan 40 mg QD Telmisartan 80 mg QD	Enalapril 20 mg QD	12	-11.6/9.3 vs. -11.8/9.7 vs. -8.2/7.2
Telmisartan 80 mg QD	Lisinopril 20 mg QD	8	-9.3/8.3 vs. -15.1/9.3
Telmisartan 40-160 mg QD +/- HCTZ 12.5-25 mg	Lisinopril 10-40 mg QD +/- HCTZ 12.5-25 mg	52	-21.1/16.3 vs. -19.3/15.4
Irbesartan 150-300 mg QD[40] +/- HCTZ +/- nifedipine 30-60 mg/day +/- atenolol 50-100 mg/day	Enalapril 20-40 mg QD +/- HCTZ +/- nifedipine 30-60 mg/day +/- atenolol 50-100 mg/day	12	-40.1/29.6 vs. -39.3/30.5

6. **Outcomes Studies:**[43-53] As stated, all ARBs have been documented to be efficacious in lowering blood pressure. A few ARBs have been evaluated beyond blood pressure control to determine if these agents can reduce morbidity and/or mortality. Not all of these studies assessed an ARB in the same patient type; also, the comparative agents have not been the same (i.e., placebo, calcium channel blocker, ACE inhibitor or beta-receptor antagonist). The value of ARBs over ACE inhibitors in reducing morbidity and mortality remains inconclusive.

7. **Safety:** The studies that directly compared one ARB to another reported similar side effects among these agents. No ARB was consistently reported to have a higher incidence of side effects compared to another. In addition, these agents did not affect biochemical markers that included liver function, blood glucose, hemoglobin, or platelet counts. Hyperkalemia may occur with all ARBs and the incidence does not appear to be greater with any specific ARB. Cough has been reported with all of the ARBs; however, the side effect occurs less frequent that with ACE inhibitors.[1-9] Most patients experiencing ACE-inhibitor cough may be treated with an ARB; although, some patients have reported cough after therapy was changed from an ACE inhibitor to an ARB.[20,54,55] The following table displays some safety data regarding the ARBs. All of the ARBs are contraindicated in persons hypersensitive to any component of the product.[3-9]

Generic Name	Warnings	Precaution
Candesartan[3]	Fetal/Neonatal Morbidity and Mortality; Hypotension in volume- and salt-depleted patients	Impaired hepatic function; Impaired renal function
Eprosartan[4]	Fetal/Neonatal Morbidity and Mortality; Hypotension in volume- or salt-depleted patients	Impaired renal function
Irbesartan[5]	Fetal/Neonatal Morbidity and Mortality; Hypotension in volume- or salt-depleted patients	Impaired renal function
Losartan[6]	Fetal/Neonatal Morbidity and Mortality; Hypotension in volume-depleted patients	Hypersensitivity: angioedema; Impaired renal function; Electrolyte imbalance
Olmesartan[7]	Fetal/Neonatal Morbidity and Mortality; Hypotension in volume- or salt-depleted patients	Impaired renal function
Telmisartan[8]	Hypotension in volume-depleted patients	Impaired hepatic function; Impaired renal function
Valsartan[9]	Fetal/Neonatal Morbidity and Mortality; Hypotension; Hypotension in patients with HF	Combination of valsartan, ACE inhibitor, and beta blocker is not recommended in patients with HF; Impaired renal function: HF, hypertension; Impaired hepatic function

8. **Drug Interactions:** The following table displays whether each ARB is metabolized by the cytochrome P450 enzyme system or the effects of the ARB on this system. According to the information, the ARBs have a low potential to interact with other medications via this pathway. Patients should not take an ARB with potassium sparing diuretics, potassium supplements, or potassium salt substitutes (reduce risk of increasing serum potassium levels). The ARBs do not appear to have any interactions with digoxin or warfarin.[3-9,56]

Generic Name	Metabolism	Effects on CYP450
Candesartan	Minimal CYP450	None
Eprosartan	Not by CYP450	None
Irbesartan	Minimal CYP450 2C9	None
Losartan	CYP450 2C9 and 3A4	Potent 3A4 inhibitors and 2C9 may reduce the formation of the active metabolite of losartan
Olmesartan	Not by CYP450	None
Telmisartan	Not by CYP450	Minor inhibition of 2C9
Valsartan	Minimal CYP450	Not known

9. Dosing: The following table displays the dosing regimens for each ARB. The ARBs are typically dosed once daily; the daily dose of selected ARBs may be divided BID. All of these agents can be taken with or without food. Dosage adjustments for age, impaired renal function and impaired hepatic function are not needed for most of these agents.

Generic Name (Brand Name)	Usual Starting Regimen	Usual Max Daily Dose	Dose Adjustments	Food Effects
Candesartan (Atacand)	16 mg once daily	32 mg (dose may be divided BID)	None need in: elderly; impaired renal function; Lower dose with impaired hepatic function should be considered	None
Eprosartan (Teveten)	600 mg once daily	800 mg (dose may be divided BID)	None need in: elderly; impaired renal and/or hepatic function	None
Irbesartan (Avapro)	HTN: 150 mg QD DM: 300 mg QD	300 mg	None need in: elderly; impaired renal and/or hepatic function	None
Losartan (Cozaar)	50 mg once daily	100 mg (dose may be divided BID)	None need in: elderly; impaired renal function; Lower dose with impaired hepatic function	None
Olmesartan (Benicar)	20 mg once daily	40 mg	None need in: elderly; impaired renal and/or hepatic function	None
Telmisartan (Micardis)	40 mg once daily	80 mg	None need in elderly or impaired renal function; use cautiously in hepatic dysfunction	None
Valsartan (Diovan)	HTN: 80-160 mg QD HF: 40 mg BID	320 mg 320 mg	None need in: elderly; impaired renal and/or hepatic function	None

10. Comments: The ARBs are efficacious agents to lower blood pressure and are associated with a low incidence of adverse effects. Collectively evaluating the hypertension studies directly comparing one ARB to another ARB, the results indicate no single ARB can be claimed to have significant clinical advantage in terms of efficacy and/or safety. In addition, results of clinical trials report ARBs to be no different, on average, in lowering blood pressure than ACE inhibitors. Many guidelines recommend an ACE inhibitor as initial therapy for patients with hypertension and coexisting disease. For instance, the JNC-7 recognizes six disease states as compelling indications for individual drug classes. ACE inhibitors are recommended as an initial therapeutic option for all six while ARBs are recommended for only three of these disease states. Until additional study results are published and analyzed, no ARB is recommended for to the P&T Committee for preferred drug status.

11. Recommendation for the Angiotensin Receptor Antagonists (ARBs): No brand name ARB offers any significant clinical advantage in general use over another ARB or the ACE inhibitors. No brand name ARB is recommended to the P&T Committee for preferred drug status.

12. References: On file.

J. Combination Products

1. Comments: The goal of antihypertensive therapy is to decrease blood pressure (BP) and reduce hypertension-associated morbidity and mortality. Most, if not all, patients will require drug therapy, which is usually initiated as monotherapy. Most all hypertensive guidelines recommend a diuretic as initial therapy (unless otherwise contraindicated) since evidence is available that documents a reduction in mortality and morbidity in hypertensive patients. However, other drug therapy may be prescribed for hypertensive patients with compelling indications (e.g., HF, post-MI). For instance, ACE inhibitors are effective for hypertensive patients with coexisting heart failure.[1-6]

Data are available that indicates 50-60% of patients will respond to initial drug therapy for hypertension.[1-5] However if the BP lowering effect to the initial drug choice is inadequate after reaching the full medication dose, the following two options should be considered: 1) if the patient is tolerating the first medication, add a second drug from another class, or 2) if the patient is having significant adverse effects or no response, substitute an agent from another class. Approximately 45% of previously uncontrolled patients achieve hypertension control after being switched to a second drug.[7,8] However, patients with severe hypertension at the time of diagnosis may require more than one medication. According to the JNC-7 report, "when BP is more than 20/10 mmHg above goal, consideration should be given to initiating therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations".[1]

Results of studies indicate that combination therapy is required to lower DBP < 90 mmHg or reduce cardiovascular events, especially in diabetic patients. Greater than 80% of patients respond to combination therapy for BP control. The most common reason for dual therapy is that monotherapy usually does not reduce the BP to significant enough levels. For patients whose SBP/DBP is > 160 / 100 mmHg, the addition of a second drug is usually required. The use of additional drugs from a class other than the initial choice will decrease the SBP/ DBP to 140/90 mmHg in approximately 85% of patients. If a diuretic is not chosen initially, then a diuretic is the second step agent because its addition will enhance the effects of other drugs used.[7,9,10]

Adding a second antihypertensive agent may increase side effects; low doses of medications that compliment each other usually decrease BP to a great extent (i.e., synergistic or additive effect) than monotherapy. Since hypertension is a multifactorial disease, the use of more than one medication that inhibit different pathophysiological pathways compliment each other. Advantages of combination therapy include: use of lower doses of component drugs; decrease the incidence and magnitude of clinical and metabolic side effects.[10,11] In fact, some clinicians suggest two low-dose antihypertensive medications rather than high-dose monotherapy.[8,9]

Thiazides are commonly selected for combination antihypertensive therapy. These agents increase the urinary excretion of sodium and chloride; in addition, potassium and bicarbonate excretion also are increased. During initial therapy, cardiac output decrease and extracellular volume diminishes. With chronic therapy, cardiac output normalizes, peripheral vascular resistance falls and there is a persistent small reduction in extracellular volume. Although indapamide is classified chemically as an indoline diuretic, this agent has similar pharmacological properties as thiazides.[12,13]

Diuretics have been associated with a decrease in cerebrovascular and cardiovascular events.[7,8,14,15] However, the prescribing of these agents has declined over the past few years.[15,16] Reasons for this include minimal promotion by pharmaceutical companies due to patent expirations, extensive promotion of branded antihypertensive medications, and myths/misconceptions of diuretics. Data are present to "counter" the myths/misconceptions about diuretic therapy. Data document that CHD morbidity and

mortality decrease to a greater extent in diabetics treated with diuretics than placebo; Hypokalemia is less common with low HCTZ doses of 12.5 to 25 mg/day and will be minimized if combined with an ACE inhibitor, amiloride, triamterene, or spironolactone.[15] Based upon these data, diuretics are effective agents for antihypertensive therapy, especially as initial therapy (even in the elderly and diabetic patients).[14,15] In fact, failing to incorporate a diuretic in the treatment of hypertension may prevent the classification of a patient as having resistant hypertension.[1,8]

2. Products: The following tables display the available combination antihypertensive products.

A. Diuretic Combination

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus spironolactone	25 or 50 mg 25 or 50 mg	Aldactazide	Yes
HCTZ plus triamterene	25 or 50 mg 37.5, 50 or 75 mg	Dyazide Maxzide	Yes
HCTZ plus amiloride	50 mg 5 mg	Moduretic	Yes

Recommendation for Diuretic Combination Review: More similarities than differences in efficacy, safety and dosing are present among the diuretic sub-classes. Many indistinguishable clinical drug characteristics are present between the multi-source and brand name agents within each subclass. No brand name diuretic combination product offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) diuretic combination products listed above. No brand name diuretic combination product is recommended to the P&T Committee for preferred drug status. Brand name diuretic combination products can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid

B. Direct Vasodilators plus Diuretic

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus hydralazine	25 or 50 mg 25 or 50 mg	Apreszide	Yes

Recommendation for Direct Vasodilator plus Diuretic Combination Review: No brand name direct vasodilator plus diuretic combination product offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) direct vasodilator plus diuretic product listed above. No brand name direct vasodilator plus diuretic combination products are recommended to the P&T Committee for preferred drug status. Brand name single entity direct vasodilator plus diuretic combination products can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid

C. Central Alpha-Adrenergic Agonist plus Diuretic

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus methyldopa	15, 25, 30 or 50 mg 250 or 500 mg	Aldoril	Yes
Chlorthalidone plus clonidine	15 mg 0.1, 0.2, or 0.3 mg	Combipress	Yes

Recommendation for the Central Alpha-Adrenergic Agonist plus Diuretic Combination Review: No brand name central alpha-adrenergic agonist plus diuretic combination product offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) central alpha-adrenergic agonist plus diuretic combination products listed above. No brand name central alpha-adrenergic agonist plus diuretic combination products are recommended to the P&T Committee for preferred drug status. Brand name central alpha-adrenergic agonist plus diuretic combination products can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

D. Beta-Adrenergic Receptor Antagonist plus Diuretic

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus bisoprolol	6.25 mg 2.5, 5, 10 mg	Ziac	Yes
HCTZ plus metoprolol	25 or 50 mg 50 or 100 mg	Lopressor HCT	No
HCTZ plus propranolol (immediate release)	25 mg 40 or 80 mg	Inderide	Yes
HCTZ plus propranolol (extended release)	50 mg 80, 120, or 160 mg	Inderide LA	No
HCTZ plus timolol	25 mg 10 mg	Timolide	No
Chlorthalidone plus atenolol	25 mg 50 or 100 mg	Tenoretic	Yes

Comment: The combination of a beta-receptor antagonist plus diuretic (BB/D) is considered to be additive in the antihypertensive effect.[9,10] The BB/D combination can increase the response rate of therapy up to 20-30% compared to monotherapy.[17] Beta-receptor antagonists decrease the sodium excretion which is reversed by the diuretic. In addition, the stimulation of the renin release by the kidneys induced by the diuretic is suppressed by the beta-receptor antagonist. One specific patient population that could benefit from the BB/D combination is African-American hypertensive patients, who have suppressed response to beta-receptor antagonists. In addition, the potassium loss induced by the BB/D combination is not a consistent finding, especially when the diuretic daily dose does not exceed 25 mg.[9]

Recommendation for the Beta-Adrenergic Receptor Antagonist plus Diuretic Combination Review: More similarities than differences in efficacy, safety and dosing are present among this antihypertensive medication class. Many indistinguishable clinical drug characteristics are present between the multi-source and brand name agents within this class. No brand name BB/D combination product offers any significant clinical advantage in general use over the drugs, strengths and

dosage forms of multi-source (i.e., generic) BB/D combination products listed above. No brand name BB/D combination products is recommended to the P&T Committee for preferred drug status. Brand name BB/D combination products can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid

E. Calcium Channel Antagonist plus ACE inhibitor

Ingredients	Strength	Brand Name Example	Generic Available
Amlodipine plus benazepril	2.5 or 5 mg 10 or 20 mg	Lotrel	No
Felodipine plus enalapril	2.5 or 5 mg 5 mg	Lexxel	No
Verapamil-extended release plus trandolapril	180 or 240 mg 1, 2 or 4 mg	Tarka	No

Recommendation for the Calcium Channel Antagonist plus ACE Inhibitor Combination Review: No brand name CCB/ACEI combination product has been shown to offer any significant clinical advantage in general use over either agent administered as a separate dosage form. No brand name CCB/ACEI combination product is recommended to the P&T Committee for preferred drug status.

F. ACE Inhibitor plus Diuretic

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus benazepril	6.25, 12.5 or 25 mg 5, 10 or 20 mg	Lotensin HCT	No
HCTZ plus captopril	15 or 25 mg 25 or 50 mg	Capozide	Yes
HCTZ plus enalapril	12.5 or 25 mg 5 or 10 mg	Vaseretic	Yes
HCTZ plus fosinopril	12.5 mg 10 or 20 mg	Monopril HCT	No
HCTZ plus lisinopril	12.5 or 25 mg 10 or 20 mg	Prinzide Zestoretic	Yes
HCTZ plus moexipril	12.5 or 25 mg 7.5 or 15 mg	Uniretic	No
HCTZ plus quinapril	12.5 or 25 mg 10 or 20 mg	Accuretic	No

Comment: The ACE inhibitor plus diuretic (ACEI/D) combination is considered to be synergistic in antihypertensive effect. The ACE inhibitor will enhance the natriuretic effect of the diuretic and also antagonize the renin stimulation and potassium loss.[9] In addition, the diuretics increase the activity of the renin-angiotensin system that enhances the ACE inhibitor effect.[7,9] Also, African-American hypertensive patients respond to this combination due to the stimulated plasma renin activation via volume depletion. Furthermore, ACEI/D combinations prevent or reverse the minimal effects of diuretics on serum glucose and lipids.[7,9] Lastly, the combination of captopril with a diuretic allows for the dosing interval to decrease from TID to BID (or even once daily).[10,17] The addition of a diuretic, even in as low a dose as 6.25 mg of HCTZ, enhances the efficacy of an ACE inhibitor, normalizing BP in an additional 20-25% of

patients with stage 1 or 2 hypertension. Low doses of diuretics (6.25, 12.5 mg) are generally recommended versus high doses since diuretics effectively reduce BP at doses much lower than initially recommended, side effects are better tolerated, and metabolic/electrolyte abnormalities commonly associated with diuretic therapy are dose-dependent and are uncommon at lower doses. According to studies that evaluated HCTZ doses of 6.25 mg per day, the BP reductions were less than those that occurred with 12.5 mg or 25 mg. Nevertheless, 6.25 mg of HCTZ used in combination with another drug regimen resulted in decreases greater than that measured with higher-dose monotherapy of either of the two other agents.[7,9] In general trials, BP is normalized within 4 weeks for up to 98% of subjects receiving the ACEI/D combination.[10]

Recommendation for the ACE Inhibitor plus Diuretic Combination Review: More similarities than differences in efficacy, safety and dosing are present among the ACE inhibitor/diuretic combinations. Many indistinguishable clinical characteristics are present between the multi-source and brand name agents within this class. No brand name combination ACEI/D formulations are recommended to the P&T Committee for preferred drug status since no information is available to document greater or significant clinical advantage over non-brand name ACEI/D combination products. No brand name ACEI/D combination product appears to offer any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) ACEI/D combination product listed above. Brand name single entity ACEI/D combination products can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price "competitive" point will be determined by AL Medicaid.

G. ARB plus Diuretic

Ingredients	Strength	Brand Name Example	Generic Available
HCTZ plus candesartan	12.5 mg 16 or 32 mg	Atacand HCT	No
HCTZ plus eprosartan	12.5 or 25 mg 600 mg	Teveten HCT	No
HCTZ plus irbesartan	12.5 mg 150 or 300 mg	Avalide	No
HCTZ plus losartan	12.5 or 25 mg 50 or 100 mg	Hyzaar	No
HCTZ plus olmesartan	12.5 or 25 mg 20 or 40 mg	Benicar HCT	No
HCTZ plus telmisartan	12.5 mg 40 or 80 mg	Micardis HCT	No
HCTZ plus valsartan	12.5 or 25 mg 80 or 160 mg	Diovan HCT	No

Recommendation for the ARB plus Diuretic Combination Review: No brand name ARB/Diuretic combination product has been shown to offer any significant clinical advantage in general use over either agent administered as a separate dosage form. No brand name ARB plus diuretic combination product is recommended to the P&T Committee for preferred drug status. .

3. References: On file.

2. Skeletal Muscle Relaxants

A. Products: The following table displays the available skeletal muscle relaxants.[1-3]

Generic Name	Brand Name	Generic Available
Baclofen	Lioresal	Yes
Carisoprodol	Soma	Yes
Chlorzoxazone	Parafon Forte DSC	Yes
Cyclobenzaprine	Flexeril	Yes - 10 mg No - 5 mg
Dantrolene	Dantrium	No
Metaxalone	Skelaxin	No
Methocarbamol	Robaxin	Yes
Orphenadrine citrate	Norflex	Yes
Tizanidine	Zanaflex	Yes

B. Pharmacology: The following table displays the pharmacological effects of the skeletal muscle relaxants.[1,2,4-8]

Agent	CNS Depressant	Direct Effect on Skeletal Muscle	Other
Baclofen			▪ Blocks afferent pathways on the spinal cord ▪ Stimulates GABA-B receptor
Carisoprodol	x		
Chlorzoxazone	x		
Cyclobenzaprine	x		▪ Anticholinergic activity
Dantrolene		x	
Metaxalone	x		

Agent	CNS Depressant	Direct Effect on Skeletal Muscle	Other
Methocarbamol	x		
Orphenadrine citrate			▪ Analgesic activity ▪ Anticholinergic activity ▪ Some local antihistaminic and anesthetic action
Tizanidine			▪ Centrally-acting alpha$_2$-adrenergic agonist

C. Indications: The following table displays the FDA-approved indications for the skeletal muscle relaxants.[1-3,5]

Agent	Indications			
	Muscle Spasticity	Adjunct Therapy	Tetanus	Other
Baclofen	x			▪ Relief of flexor spasms and concomitant pain, clonus, and muscular rigidity ▪ Improve bowel and bladder function in some patients with spinal lesions
Carisoprodol		x		
Chlorzoxazone		x		
Cyclobenzaprine		x	x	

Dantrolene	x			▪ Post-crisis malignant hyperthermia Prevent malignant hyperthermia
Metaxalone		x		
Methocarbamol		x	x	
Orphenadrine citrate		x	x	
Tizanidine	x			▪ Skeletal muscle spasms and clonus

Adjunct therapy refers to the treatment of musculoskeletal conditions that cause muscle spasms and tenderness (e.g., mechanical low back or neck pain). Local factors are involved in affecting the muscle groups; increased tone or reflex is usually absent. Musculoskeletal conditions, which are primarily acute and more common than spasticity, can cause significant pain and disability.[14]

D. Unlabeled Uses: The following table displays the unlabeled uses for the skeletal muscle relaxants.[1-3,5,9,10]

Agent	Unlabeled Uses
Baclofen	▪ Treat trigeminal neuralgia ▪ Manage Huntington's chorea ▪ Decrease spasticity in patients with cerebral lesions, cerebral palsy, or rheumatic disorders ▪ Decrease spasticity in cerebrovascular stroke ▪ Schizophrenic disorder
Cyclobenzaprine	▪ Fibromyalgia syndrome
Dantrolene	▪ Manage neuroleptic malignant syndrome ▪ Fulminant hypermetabolic reaction ▪ Reduce strength of succinylcholine-induced muscle Fasciculations intra-operatively Reduce incidence of post-op muscle pain
Tizanidine	▪ Headaches: chronic tension or cluster ▪ Adjunct in anesthesia

E. Pharmacokinetics: The following table displays selected pharmacokinetic parameters of the skeletal muscle relaxants.[4,5,11]

	Onset of Action	Duration of Action	Absorption	Half-Life	Metabolism	Excretion
Baclofen	3-4 days*		Rapid	~3.5 hrs	Hepatic (15% dose)	Urine and fece (85% unchange
Carisoprodol	~30 min	4-6 hrs		8 hrs.	Hepatic	Urine
Chlorzoxazone	~1 hr	3-4 hrs	Readily	~1 hr	Extensively hepatic via glucoronidation	Urine as conjugates
Cyclobenzaprine	~1 hr	8 to > 24 hrs	Complete	1-3 days	Hepatic; may undergo enterohepatic circulation	Urine (as inacti metabolites); feces (as unchanged dru
Dantrolene	n/a		Slow and incomplete	8.7 hrs	Hepatic	Feces (45%-50%); Urine (25% unchanged dru and metabolite
Metaxalone	~1 hr	~4-6 hrs	Not established; food may	9 hrs†	Hepatic	Urine (as metabolites)

			increase			
Methocarbamol	~30 min			1-2 hrs	Hepatic	Urine (as metabolites)
Orphenadrine citrate	n/a	4-6 hrs		14 hrs	Almost completely metabolized to 8 metabolites	Urine, principal (as metabolites
Tizanidine	n/a	3-6 hrs		2.5 hrs	95% metabolized	

* May vary from hours to weeks † 2-3 hrs with high fat meals

F. Safety: The following table displays the safety concerns/considerations for the skeletal muscle relaxants.[4,12]

Agent	Considerations
Baclofen	• Hypotension, seizures, and muscle weakness are common adverse effects • Reduce dose in elderly and pts. with renal impairment
Carisoprodol	• Controlled substance IV in Alabama • Metabolized to meprobamate • Caution when discontinuing due to psychological dependency • Reduce dose in patients with hepatic insufficiency
Chlorzoxazone	• Can cause unpredictable, fatal hepatic toxicity • May turn urine orange or purple-red
Cyclobenzaprine	• Anticholinergic effects • Duration is 2 to 3 weeks • Should not be used in patients on MAO inhibitors or within 14 days after their discontinuation
Dantrolene	• Black box warning for hepatotoxicity • Muscle weakness is a common adverse effect • Maximum duration is 45 days
Metaxalone	• Obtain LFTs for pre-existing liver damage • Should not be used in patients with known tendency to drug-induced hemolytic anemia or other anemias

F. Safety (continued): The following table displays the safety concerns/considerations for the skeletal muscle relaxants.[4,12]

Agent	Considerations
Methocarbamol	• May turn urine black, green, or brown
Orphenadrine citrate	• Anticholinergic effects
Tizanidine	• Common side effects include hypotension and muscle weakness • Use with caution in renally impaired patients

G. Efficacy: The majority of clinical trials evaluating a skeletal muscle relaxant to treat musculoskeletal conditions are dated. Results of most trials report the skeletal muscle relaxant are more efficacious than placebo. A few studies have directly compared two agents from this medication class (e.g., cyclobenzaprine vs. carisoprodol). According to the collective results, no agent can be considered the agent-of-choice in terms of efficacy and safety. Data regarding metaxalone indicate this agent to have minimal to no efficacy differences than placebo.

Recently a cyclobenzaprine 5 mg formulation has been marketed. The efficacy and tolerability of this dosage strength has been directly compared to cyclobenzaprine 2.5 mg and 10 mg plus placebo in patients with acute musculoskeletal spasm of the lumbar or cervical region.[13] Two double-blinded clinical trials assessed the clinical global

impression of change, medication helpfulness, and relief from starting backache on days 3 and 7 assessed on a patient-rated scale. Secondary endpoints included degree of relief from starting backache before the evening dose of medication (as recorded on the diary card) and the physician's rating of muscle spasm. Patient inclusion criteria included adults with acute, physician-rated moderate or moderately severe painful muscle spasm of the lumbar and/or cervical region with a duration of current episode ≤ 14 days. In the first study, patients were randomized to either cyclobenzaprine 5 mg, 10 mg or placebo TID for 7 days. The second study compared cyclobenzaprine 2.5 mg, 5 mg and placebo TID. The mean age of the patients in both studies was ~42 years, 86-90% were Caucasian and 55-60% were male. Study 1 reported no differences in the pairwise comparisons between cyclobenzaprine 5 and 10 mg; although, both were significantly better than placebo on all measures at visits 2 and 3 ($p \leq 0.001$). For instance, mean patient-rated clinical global impression of change scores were 2.82 to 2.88 for both cyclobenzaprine groups at the last visit (score of 4 indicated "marked improvement"); mean relief of starting backache score at day 7 was 2.38 (score of 3 indicated "a lot of relief"). Onset of efficacy was observed within 24 to 48 hours from the initiation of treatment with the cyclobenzaprine 5 mg group; whereas, the cyclobenzaprine 10 mg group experienced onset of relief after the first 2 doses. The adverse effects of both studies evaluating cyclobenzaprine 5 mg were pooled. Somnolence was the most commonly reported side effect (29%, 38% and 10% for cyclobenzaprine 5 mg, 10 mg and placebo, respectively). Dry mouth (21%, 32% and 7%) and headache (5%, 5%, 8%) were the other most common side effects. The results of these trials demonstrate the efficacy of cyclobenzaprine 5 and 10 mg in the management of acute musculoskeletal spasm of the back or neck; cyclobenzaprine 2.5 mg TID was not statistically different from placebo. Cyclobenzaprine 5 mg TID was as effective as 10 mg TID, and was associated with a modestly lower incidence of sedation.

H. Dosage: The following table displays the usual dosage regimen for the skeletal muscle relaxants.[1-3,9]

Generic	Brand Name	Dose	Frequency
Baclofen	Lioresal	5 mg	TID Dose may be increased by 5 mg/ dose every 3 days to a max. of 80 mg/day
Carisoprodol	Soma	350 mg	TID and QHS
Chlorzoxazone	Parafon Forte DSC	250 - 750 mg	TID - QID
Cyclobenzaprine	Flexeril	10 mg	TID
Dantrolene	Dantrium	100 mg	TID Follows a titration schedule
Metaxalone	Skelaxin	800 mg	TID - QID
Methocarbamol	Robaxin	750 mg - 1.5 g	TID - QID
Orphenadrine	Norflex	100 mg	BID (am and pm)
Tizanidine	Zanaflex	8 mg	TID - QID Max: 36 mg/day

I. Comments: Skeletal muscle relaxants are most commonly prescribed to treat conditions that include spasticity (due to neurological conditions) and musculoskeletal conditions (which result in muscle spasms [i.e., mechanical low back or neck pain]). The majority of literature that has been recently published evaluates tizanidine; otherwise minimal literature has been published recently comparing or evaluating these agents as adjuncts in treating musculoskeletal conditions. According to the available information, no specific agent from this class has been documented to produce a greater therapeutic effect than another agent. Most of these agents have been compared to placebo.

Dantrolene has a unique pharmacology compared to the other agents in the class. Dantrolene is not commonly prescribed as an adjunct for musculoskeletal conditions (e.g., “muscle pull”) as other agents (e.g., methocarbamol, metaxalone). No literature has been published recently evaluating metaxalone. Studies available report metaxalone to be no more effective than placebo. A 5-mg dosage strength of cyclobenzaprine has recently been marketed. According to the clinical trials evaluating various cyclobenzaprine strengths (2.5, 5, 10 mg) to placebo, the efficacy of the 5-mg dosage form is no different than the 10-mg formulation. The incidence of side effects is slightly lower with the 5-mg tablet than with the 10-mg tablet (e.g., somnolence: 29%, 38% and 10% for cyclobenzaprine 5 mg, 10 mg and placebo, respectively).

J. Recommendation for the Skeletal Muscle Relaxants: No brand name skeletal muscle relaxant offers any significant clinical advantage in general use over the drugs, strengths and dosage forms of multi-source (i.e., generic) skeletal muscle relaxant listed in section A above. No brand name skeletal muscle relaxants are recommended to the P&T Committee for preferred drug status. Brand name single entity skeletal muscle relaxants can be considered for preferred status if the price of the brand name agent is competitive to a pharmaceutically and/or therapeutically equivalent multi-source (i.e., generic) formulation. The price “competitive” point will be determined by AL Medicaid

J. References: On file.